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OF
RELAPSING FEVER.

BY

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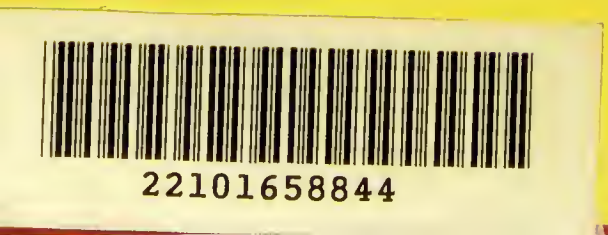

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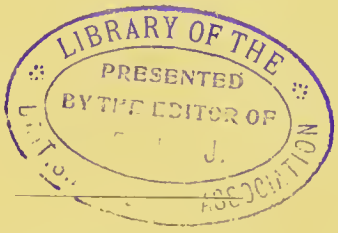

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PREFACE.

In 1891 I had an opportunity of investigating the latter end of an outbreak of Relapsing Fever which occurred among the workmen engaged in the Khojak Tunnel Works, and availing myself of this opportunity I undertook a series of examinations of the blood of the patients suffering from this disease. An account of my results was submitted to the Surgeon-General with the Government of India in a report which was subsequently published in the *Indian Medical Gazette*. I did not pursue my investigations with the object of making any contributions to the literature of the subject, my object only being to offer sufficient evidence as to the existence of the disease ; owing to this, I did not attempt to make any drawings of my preparations and I regret to say that those preparations which I retained have since deteriorated from climatic influences. I have whenever it has been considered necessary filled up this deficiency by borrowing from other works.

During my recent furlough in England I took an opportunity of looking up the literature of Relapsing Fever, and was surprised to find, that since Carter's excellent monograph on "Spirillum Fever" [76] published in 1882, no contribution has been

made to the subject in the English language. This is accounted for by the comparative absence of the disease from Great Britain; on the other hand, we have evidence that the disease is frequently prevalent in India.

That the disease was frequently seen before the Bombay outbreak investigated by Carter can be gathered from Dr. Bryden's Statistical Report of 1877, and from a small work on "Relapsing Fever in India" by Surgeon-Major R. T. Lyons. Since 1882 Carter has published a few cases admitted into the Bombay Hospitals in the Transactions of the Medical and Physical Society of Bombay (Vol. VI of 1885 and Vol. XI of 1888), and in the Reports of the Sanitary Commissioner with the Government of India are to be found frequent references to outbreaks of the disease either among the jail or free population.

Since the publication of Carter's work a good many important contributions have appeared chiefly from Russian sources; but to gain any information it is necessary to look over a fairly large number of continental journals, a procedure which is out of the question in India. The clinical aspects of the disease are generally well described in the ordinary text-books; on the other hand, but little is mentioned of the spirillum and the pathological changes produced by it. It has appeared to me that it would be advantageous to bring

together our present knowledge of the pathology of the disease. The more frequent examination of the blood of patients suffering from febrile diseases in India which is likely to follow the recent developments in malarial pathology will no doubt occasionally lead to the discovery of the Spirillum of Relapsing Fever. I have in this little work given considerable attention to the methods which should be employed for the detection of this organism.

I have consulted most of the literature of Relapsing Fever published since the Spirillum was first described in 1873, and I trust that the bibliography given at the end of this work may be of use to subsequent workers. When necessity arises to refer to any work published anterior to 1873 it will be given as a footnote, in all other instances the small number indicates the work mentioned at the end of the book.

I have to tender my best thanks to M. Duclaux, Director of the "Annales de l'Institut Pasteur" for permission to reproduce Plates I and III ; and to Professor Lukjanow, Director of the Imperial Institute for Experimental Medicine, St. Petersburg (for Professor Ouskow), for permission to reproduce Plate II.

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Chapter I.

General Remarks—Evidences for considering the Spirillum the cause of Relapsing Fever.

Although in 1843 Dr. Henderson of Edinburgh, had taught us how to differentiate relapsing fever from other fevers of a continued type, for many years a considerable amount of difficulty appears to have been experienced in accurately diagnosing the disease. In 1868 Dr. Carl Obermeier, an Assistant of Professor Virchow, had an opportunity of investigating the first epidemic of relapsing fever, which occurred in Berlin, and although he seems then to have believed that a parasite was found in the blood, he evidently had not sufficiently convinced himself of its existence as in his account of 82 cases published by him in Virchow's Archives, Vol. 46 of 1869, he does not allude to the subject. In 1872 the occurrence of a second epidemic in Berlin gave Obermeier a further opportunity of carrying out observations and of firmly establishing the existence of a *spirochæte* or *spirillum* in the blood. His first account of the parasite was published on 1st March 1873. [1] His observations were soon confirmed by Engel, [3] Weigert, [5] Bliesener, [6] and others, and though at first many observers failed to observe the spirillum, and others who

succeeded in finding it did not admit of its being specific to the disease as a spirillum had been found in the mouth, and in caries and noma (Mannaseim), [28] at the present time few entertain, or should entertain, any doubt that the spirillum of Obermeier is found in the blood of patients suffering from relapsing fever. Not only does the presence of the spirillum afford a ready method of diagnosing the disease ; but it has helped to settle that the disease first described by Greissinger in 1852 as " Typhus Biliosus" is nothing but relapsing fever attended with well marked jaundice, a complication which appears to have been particularly prevalent in some epidemics.

That the spirillum is the cause of the disease admits of no doubt on the following grounds:—

1. The spirillum is found in the blood of patients suffering from relapsing fever *only*.

2. The spirillum is present for the first time immediately before the commencement of symptoms.

3. Whilst the spirillum is present in the blood the symptoms continue.

4. The disappearance of the spirillum is rapidly followed by the cessation of symptoms.

5. Inoculation of blood containing the spirillum into healthy men, or monkeys, is followed by a typical attack of the disease.

To complete the chain of evidence as to the spirillum being the cause of relapsing fever, the

cultivation of the parasite outside the body is still wanting.

The disease was first produced in man by inoculation in 1874, Dr. Münch [11] of Moscow, having inoculated himself, a typical attack ensuing. In 1876 Moczutkowsky [24] published the result of his inoculations in individuals who had allowed themselves to be inoculated. His conclusions are so important that I give them at some length.

"The artificially inoculated recurrent fever differed in no respects from the acquired disease; either in clinical appearances, in intensity, duration, and in the number of attacks.

The inoculated recurrent fever was not found to increase in intensity with each subsequent inoculation.

From the inoculation of recurrent fever nothing but recurrent fever is produced and not any other infectious disease.

The incubation period lasts not less than five or more than eight days.

The duration of apyrexia corresponds approximately to the duration of the inoculation period.

The inoculation was only successful when the blood was taken during the attack."

In 1887 Metschnikoff [104] also succeeded in inoculating himself producing a typical attack He inoculated himself on 5th and 7th March, the pyrexia commencing on the 12th.

Up to 1879 all attempts to produce the disease in animals had failed; but in this year Dr. Vandyke-Carter [50a] of the Bombay Medical Service, first succeeded in successfully reproducing the disease from man into monkeys, and from monkeys into monkeys. His results were confirmed in the same year by Koch [38] and have since been repeated by Metschnikoff [104] in 1887, Schwalowski [121] and Soudakewitch ([116]/[123]) in 1890, and by Tictin ([127]/[134]) in 1893.

The monkeys experimented on have been *Macaccus Radiatus* (*Sinicus*), *Macaccus Erythreus* (*rhesus*), *Macaccus Nemestrinus*, *Macaccus Cynomolgus*, *Cercocebus fuliginosus*, *Cercopithecus Griseoviridis*, *Cercopithecus ruber* (*patas*), *Semnopithecus Entellus*.

Infection has been produced by the inoculation into the thigh, or back, of 3—20 minims of defibrinated or pure blood. No local inflammation is produced by the inoculation, and the animal generally remains well until the commencement of pyrexia.

The period of incubation in monkeys is generally three days. Carter gives an average of three to four days, and a range of from 12 to 186 hours. The duration of the attack is two to four days. Carter gives from 6 hours to not more than 86 hours. Monkeys, as a general rule, have no relapse. Carter ([p. 76]/[430]) only noticed a spirillar relapse in two cases on the 6th and 12th day after the first attack. He was inclined to believe that these were cases of

second spontaneous infection. None of the other experimenters have described a true relapse in monkeys, though a transient rise of temperature, without the spirillum being found, has been noticed.

All the successful experiments hitherto performed have been with blood containing the spirillum, —9 performed by Carter with blood not containing the parasite failed, likewise 7 with dried blood.

Carter believed that whilst inoculation from a severe human case did not necessarily produce a case of similar severity in the monkey, inoculation from monkey to monkey produced an intensified form of the disease accompanied by higher mortality.

That the disease in monkeys is identical to the disease seen in man is not to be doubted; but there are some important differences in the length of the incubation period, and in the duration of the attack. The usual incubation period in monkeys is roughly, four days, in man five to eight days. The duration of the attack in monkeys is two to four days, in man six to seven days. It must be remembered, too, that whilst a relapse only exceptionally takes place in monkeys, one or more relapses are the rule in man.

All attempts to reproduce the disease in sheep, horses, rabbits, guinea-pigs, fowls, pigeons, cats and dogs have hitherto proved unsuccessful.

Likewise all endeavours to artificially cultivate the spirillum have failed. Engel and Weigert noticed an apparent increase in numbers in blood

serum. Koch failed to cultivate it; but found tangled masses, and an increase in the length of the spirillum. Carter noticed a general enlargement, extension and formation of open networks, and dense aggregation and blending.

In its resistance to be artificially cultivated, the Spirillum Obermeieri has resembled many other spirilla. Up to quite recently there were few examples of this class which had been cultivated ; but with improved methods Kutscher* has lately succeeded in cultivating spirillum tenue, spirillum serpens, spirillum undula, and spirillum volutans. Kutscher's observations have been confirmed by Bonhoff†, and it is to be hoped that their success may pave the way for the successful cultivation of the Spirillum Obermeieri.

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* Zeitschrift f. Hygiene und Infectious Kranken, XX. 1 s., p. 46, 1895, and Centralb. f. Bakt and Parasitenkund, Bd. XVIII, Nos. 20 and 21, p. 614.

† Untersuchungen uber Vibrionen and Spirillen. Archiv. f. Hygiene, 1896, p. 162.

Chapter II.

Description of the Spirillum—How to detect it—Methods of staining it.

The Spirillum or Spirochœte Obermeieri is, according to Cohn's classification, a spiro-bacterium; it has hitherto never been found outside the body, and is therefore a *strict* or *obligatory* parasite. Some observers have considered the spirillum to be a protozoon, this view was first brought forward by Sakharoff in 1888 [115]. Sakharoff himself has since admitted that the appearances which led him to this belief were produced by the relapsing fever being complicated with malaria;* the same condition has also been described by Karlinski. [123a] On looking over my notes I have found occasional mention of intra-corpuscular bodies which I attribute to the same cause.

We have but few examples of pathogenic spirilla affecting man, the only others besides the *Spirillum Obermeieri* being the *Spirillum of Asiatic cholera*, and the *spirillum of cholera nostras*. In animals we likewise find few examples, namely, the *Spirillum Tyrogenum* of Deneke, the *Spirillum Metschnikovi*, and what is of importance from its being a blood parasite, and from its close resemblance with the

* Annales de l'Institut Pasteur, 1891, p. 566, foot-note.

spirillum of relapsing fever, namely, the *spirochæte anserina* found in the blood of geese by Sakharoff.* Sakharoff succeeded in reproducing the disease in a goose and a chicken, by inoculation with blood containing the parasite.

The saprophytic spirilla are numerous, and are found almost always in connection with decomposing animal or vegetable matter. Spirilla have been found in the mouth of man, with or without the presence of decayed teeth. They were also found by Billroth in pus from carious bone and in noma.

The spirillum of relapsing fever consists of long wavy flexile threads 12—43 u in length (Heydenreich), and from .3 u [87] to 1 u (Sternberg)† in thickness. Roughly the spirillum is computed to be in length equal to the diameter of $1\frac{1}{2}$ to 6 red blood corpuscles, and in thickness the width of a fibrin thread (Obermeier [1]). Engel has described spirilla the length of as much as 30 diameters of the red cells, but this was probably produced by more than one spirillum joined together.

The number of windings vary from 6 to 16, or even 20, they are pretty regular in size, the variation in this respect being slight, there are no primary and secondary curves such as are seen in the *spirillum plicatile;* the radius of the curves is between $\frac{1}{2}$ to $\frac{1}{4}$ of the diameter of a red blood

* Annales de l'Institut Pasteur, 1891, p. 564.

† Manual of Bacteriology, 1896, p. 549.

corpuscle, and varies with the motion of the spirillum. Engel stated that the later in the attack the blood is examined, the larger the spirillum is, but this is not correct, for variations both in length and in thickness are constantly found in specimens taken at various stages of the attack. In structure the spirillum is homogeneous, with slight or no tapering at the extremities ; though presumably possessing a sheath nobody has succeeded in either detecting it or in successfully staining it. Koch* has described one or more flagella at both extremities of the spirillum, more recently this has also been confirmed by Karlinski.[123a] Considerable difference of opinion has existed as to whether the spirillum displays any structure. Obermeier, for example, observed thickenings in the course of the spirillum, Carter ($_{p.\ 351}^{76}$) described a dotted or knobbed aspect in fresh blood, and beaded spirilla have been mentioned by many authors. The diagram in Plate I of Carter's monograph shows the beading at the summit of the curves, but as it were budding out of the curves. In the many examinations that I made in my cases I have frequently come across the following : If a spirillum was examined towards the end of the attack, when its motion was becoming sluggish, and of a slow undulatory, or pendulum-like character,

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* Eisenberg's Bacteriological Diagnosis.

I very frequently observed, when making examinations with an immersion lens of high N. A., magnifying not less than 800 diameters; that the summit of each curve possessed a minute dot occupying the *whole* diameter of the spirillum, this dot was somewhat bright and possessed a very faint reddish tinge On more minute examination, especially when motion was very slow, the spot was found to be visible only on flexion of the corresponding portions of the curves, this at first led me to believe that the production of this appearance might be due to optical conditions ; but its very distinct rounded and defined character, and the fact of my having observed *straight* spirillar fragments with one or more distinct dots at intervals, led me subsequently to think that these existed in the fully formed spirillum, but were only rendered visible during flexion. I failed to detect any dots in any situation but on the summit of the curves, and occasionally at the extremities of the parasite. In the living state I have never seen structures composed of super-imposed dots, though such a condition is fairly frequently seen when the spirillum has lost its vitality.

Several observers, namely, Engel, Litten, Unterberger, and Carter have described very fine spiral forms ; I have seen these before the actual development of pyrexia, but have never seen them during an attack.

During motion the spirillum occasionally assumes peculiar forms ; for example, complete circles formed by the flexion of the whole thread, or a ringed or looped appearance from flexion of one end. Obermeier first called attention to the peculiar star-shaped aggregations of spirilla, these may consist of even 60 or more individuals radiating from a centre (*vide* Plate I). These aggregations are only seen when there are many parasites in the blood. Heydenreich believed that they were produced by the adhesiveness of the parasite itself ; but the condition can be more satisfactorily explained on mechanical grounds, the spiral form which it possesses being sufficient to account for the entanglement of the individual threads ; one can often watch under the cover-glass how other spirilla which approximate the mass become entangled and thus help to add to the size of the compound structure.

The spirillum when dead alters somewhat in appearance, its contour becomes sharper, and its curves widen. I have seen fragments during the apyrexial period which were broader than the living filaments; but a dead spirillum, under the cover-glass, does not, for some time at least, show any signs of thickening. Moczutkowsky [40] gives the following description of the changes observed; 2 hours after cessation of motion they swell up uniformly, their diameter becoming almost double.

they then become cloudy; after a short while, a fine granular disintegration is apparent by which the arrangement of the detritus is almost impossible to be made out. In dry specimens beaded spirilla are frequently met with.

It is possible at first to revive a dying spirillum by warmth.

The fact that the spirillum is found in the blood, and not in the lymph ducts has led to the conclusion that it is *aërobic*. In support of this Weigert [29] says that the parasite floats on the surface of blood collected in a vessel so long as it is living, that this is not due to diminished specific gravity is shewn by the spirilla subsiding to the bottom of the glass after their vitality is lost.

Motion of the Spirillum.—The individual filaments possess the following kinds of motion :—

1. Screw, spiral, or boring motion, the whole thread moving like a corkscrew when it is being turned.

2. Undulatory motion along the whole length of the filament with progression forwards or backwards.

3. Side to side, pendulum-like, or rocking motion, the bends being in the form of curves more or less angular.

4. Tetanic motion (Münch).

In his original communication in 1873 Obermeier described the first two kinds of motion, in Engel's paper published shortly after, attention was called

to the side to side or pendulum motion, the tetanic motion was described by Münch in 1874.

Heydenreich in 1877 expressed the opinion that the spiral motion was the primary or active motion, the other forms being passive and produced by obstruction to the movements of the filaments. Some authors have believed that the pendulum motion may be caused by death of a portion of the filament, whilst the living portion by its motion produces the flexion. We have no evidence to show that a portion of the parasite can die irrespective of the remainder. It must be remembered that observations carried on under a cover-glass differ widely from the conditions in which the spirillum exists in the general circulation; but the fact that specimens examined under identical conditions show differences in the motion of the filaments, indicates, that these cannot be entirely produced by mechanical causes. The alterations in the kind of motion must be considered to be produced by the diminished vitality of the spirillum, which causes it to lose its primary motion, the spiral, and as a first stage of this diminished vitality displays the undulatory, then the pendulum, and finally the tetanic forms of motion ; the latter being nothing but temporary pauses followed by temporary energetic motion.

Weigert ($_{p.\ 589}^{5}$) first pointed out that in the early stages of the attack the axial motion of the spirillum

was prevalent, whilst the nearer to the crisis, the more common the pendulum motion became, and that at the same time motion became slower and slower. Moczutkowsky ($\frac{40}{p.\,88}$) has also made the same observation, and has also indicated that often together with the spirilla with diminished motion are others in which motion has entirely ceased. Similar remarks have been made by Laptschinsky [40] and by Paternatzki.[120] I have frequently noticed this diminution in the vitality of the filaments towards the end of the attack; it was particularly marked in two instances in which I saw a few spirilla immediately after the crisis with subnormal temperature.

The presence of flagella in the spirillum may suffice to explain its progressive motion, but no satisfactory explanation has hitherto been given as to how the spiral motion is produced. Lateral flagella have not hitherto been seen.

Detection of the Spirillum in fresh blood.—After cleansing the finger with soap and water, bathe it with strong sublimate solution (1 in 500), or in carbolic lotion (1 in 20). Then prick the finger with a needle, or with a lancet, which is much better; touch the exuded drop of blood with a cover slip, and immediately place the cover slip on a slide. Care should be taken not to exert any pressure which might likely produce currents. If the drop is a fairly large one, the blood will run out of the

margin of the slip and by coagulating will seal as it were its edges. It is best to undertake as soon as possible the microscopic examination. The spirillum can be fairly well seen with an objective magnifying about 400 diameters ; but it is best to use one magnifying 500 diameters preferably an immersion lens. Good illumination is required, and if possible an achromatic condenser. For research purposes higher immersion lenses with a fairly high N. A. are necessary.

In examining a blood specimen we naturally first focus the blood corpuscles, and we shall soon find out whether the spirillum is present or not by the commotion produced in them. If the examination has not been long delayed after the preparation was made, this quivering of the blood corpuscles gives a very strong indication of the presence of the spirillum ; a little deeper focussing of one of the intervals between the blood cells will soon reveal the actively moving spirilla. By commencing fibrillation of the plasma, the spirillum will still be found here and there in the squeezed out blood serum, and at times it will continue active for some hours.

By examination of blood specimens immediately after their preparation one is able soon to gain an acquaintance with the parasite, whilst if an attempt is made to examine dry preparations before one has learnt to recognise the spirillum, the probability is that it will be missed over and over again.

For recording purposes it is best to note the number of spirilla present in each field of the microscope; I adopted in my observations a modification of Carter's method of giving a certain meaning to the terms,—very few, few, fairly numerous, numerous, or teaming; but, on the whole, stating the number of spirilla per field is the most convenient.

If it is required to make a more prolonged examination than can be effected by the method above described, that is, by allowing the blood to coagulate along the edge of the cover slip; slightly hollowed-out slides, or a Hayem's *cellule à rigole* may be used, this has in the centre a circular disc surrounded by a hollow groove.

For more prolonged observations other methods have been used. Heydenreich used vaccine tubes which were hermetically sealed, and in this manner he states that he had been able to see spirilla alive for 130 days after the preparation was made. Moczutkowsky in 1879 used a fine pipette-shaped glass tube, in this he observed spirilla alive for 37 days. Albrecht made use of capillary tubes and Paternatzki [119] has more recently used very fine capillary tubes which, including their walls, were not thicker than an ordinary cover slip; in this manner an extremely fine layer of blood was obtained.

In any of the above ways the blood can be examined either pure, defibrinated, or mixed with $\frac{1}{2}$ per cent salt solution.

In 1890 Paternatzki first brought to notice that leeches which have imbibed blood containing the spirillum can be frozen, the spirilla within them retaining their vitality. When the leeches return to life, by placing a little salt on them, a drop of blood exudes from the proboscis, the blood can then be collected and examined under the microscope. The same observation has been made by Karlinski and others.

Although the examination of fresh blood offers a ready method for detecting the spirillum, still there are many instances in which the parasite cannot be found in fresh specimens ; from this we cannot conclude that it is absent as they have often been detected by staining the preparations when they were supposed to be absent. In making observations at frequent intervals in the day, or at night, it may sometimes not be convenient to make an immediate microscopical examination ; under such circumstances, one of the following methods can be employed :—

If it is desired to retain the blood corpuscles the preparation must be fixed before proceeding to stain it. In both Albrecht's and Gunther's method the blood corpuscles are broken up. The quickest method of fixing the hæmoglobin is either by heating the cover-glass preparation to 110° or 120° C. (Ehrlich's method), or by exposing the film to the fumes of 2 per cent osmic acid, the film may also

be fixed by treating it with alcohol and ether as in Nikiforoff's method, or by placing the wet film in saturated sublimate solution.

If good leucocyte fixation is required, the following method of fixing cover-glass preparations suggested by Dr. Gulland* may be used, the cover slip is placed in the following solution for three or four minutes:—

Absolute alcohol saturated with eosin	... 25 c.m.
Pure ether	... 25 c.m.
Sublimate in absolute alcohol (2 grm. to 10 c. c.m.	... 5 drops more or less.

After removal wash rapidly in water, stain, wash again dehydrate in absolute alcohol, clear in xylol and mount in xylol balsam.

1. *Osmic acid preparations.*—A cover slip preparation having been carefully made, as the spirillum is easily destroyed, the thin layer of blood is exposed to the fumes of two per cent. osmic acid, this causes a certain amount of alteration in the colour of the preparation making it somewhat browner, but it does not affect the structure of either the spirillum or the blood cells which remain fixed. This method though excellent and taking a short time, is in many ways inferior to the staining methods. Soudakewitch ($_{p.}^{123}_{548}$) has combined both, after exposing the blood to the fumes of $\frac{1}{2}$ per cent. osmic acid, he has stained the spirillum with aqueous solution of gentian violet.

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* British Medical Journal, 13th March 1897, p. 652.

2. *Albrecht's method* [41].—A cover-glass preparation is made and allowed to dry; a drop of glacial acetic acid is added, and after one to two minutes it is allowed to run off, wash with water, and dry again. Carter substituted ordinary acetic acid for the glacial acetic acid. The preparation can then be stained with methyl violet, or Bismark brown, or in fact by watery solution of any aniline dye. Heydenreich recommended fuschine. By means of the acetic acid the red blood corpuscles break up into globulin and hæmatin which are dissolved by the acid; the white corpuscles are likewise dissolved, and the only things evident in the preparation are the nuclei of the white cells, and the spirillum, which are stained by the aniline dyes.

3. *Gunther's method** [90 (p. 755)].—Gunther called attention to the fact that the spirillum does not stain in acid staining solutions, but in basic watery solutions of aniline. He found that methyl violet had scarcely any effect, fuschine produced slight staining, whilst, on the other hand, gentian violet produced intensive staining (100 c.c. aniline water and 11 c. c. of concentrated alcoholic solution of gentian violet), he found, however, that even with this many spirilla remained unstained.

Gunther found that by the use of acetic acid good preparations could be made as follows: make

* Mittheilt von Loeffler in den Mitth, aus dem K. Gesaudh, Bd. 1, 1881, p. 168.

a cover-glass preparation, dry it and plunge it into 5 per cent. solution of acetic acid in which it should remain for 10 seconds ; dry it, and expose it for a short while to ammonia vapour so as to neutralise the excess of acid, wash and put it into the gentian violet solution, after drying mount in xylol Canada balsam. This is an excellent method.

4. *Pastor's method* [83].—This is inferior to the above. A cover-glass preparation having been made, it is dried in a bath of heated air of a temperature of 100° c., place after in a concentrated alcoholic solution of methyl violet diluted with equal quantity of distilled water which is heated for 5—10 minutes until it begins to steam. Remove and wash, dry and clear with oil of cloves.

5. *Nikiforoff's method* [107 (p. 183)].— He recommends that a cover-glass preparation should not be made in the usual way, but that the drop of blood collected on a cover slip should be spread out by means of another cover slip held at an angle of 45°, then dry the layer of blood and place in a flask containing equal parts of absolute alcohol and ether; in this they should remain for several hours or even for a whole day. The preparation is then stained with a watery solution of any of the aniline dyes.

6. *Baschenow's method* [126].— Cover-glass preparations are stained with Magdalia Dahlia (1 drop of alcoholic solution of this violet substance in 30 c.c. of water), warm to get rid of the moisture;

after 5 minutes wash with water, dry, and mount in Canada balsam.

7. *Mamurowski's method* [128]. — A cover-glass preparation is made, dried by heat, and left for 1 to 2 hours in alcoholic saturated solution of eosin ; after it is placed in a watery solution of methylene blue for 20 to 30 minutes, wash, dry, and mount in Canada balsam. In this preparation the spirillum is stained blue, the blood cells of a rose colour.

If desirable an attempt may be made to stain the flagella of the spirillum, but it is a difficult process. Koch succeeded in staining them with hæmatoxyllin ; Löffler's or Pitfield's methods for staining flagella might be tried, the latter being perhaps the best as only one solution is used.

Chapter III.

Effects of Physical and Chemical Agents on the Spirillum.

The effects of temperature were carefully investigated by Heydenreich in 1876 [20] with the following result : *Heat.*—A temperature of 15° to 22°C. was found to be the most favourable for the continuance of life of the spirillum ; it generally lived up to a week at this temperature, and in one instance for 14 days. At a temperature of 37°, it lived only 15 to 25 hours. All temperatures above 37° (the normal) were unfavourable ; for example, at a temperature of 39·5 to 40°C. the spirillum ceased to move in 12 hours ; at a temperature of 41 to 41·7C. motion ceased in $5\frac{1}{2}$ hours ; at a temperature of 43° to 45° in 2 to 3 hours ; and at 44·5 to 46°C. motion had already ceased in $1\frac{1}{2}$ hours.

Moczutkowsky [40 (p. 198)] considered a higher temperature necessary for the destruction of the spirillum ; he found that it did not break up until it had been exposed to a temperature of above 48°C.

Paternatzki [120] has more recently carried out some experiments and found that a temperature of not more than 45°C. was sufficient to destroy the spirillum.

There appears therefore to be no doubt that a high temperature has a hindering influence on the life of the spirillum.

Cold retards the motion of the spirillum, provided the action has not been too prolonged. A temperature of 3 to 6°C. according to Heydenreich, causes cessation of motion in about ½ hour, and even after being kept at this temperature for some hours motion will again be regained. Paternatzki [119] has also shown the power of resistance against cold possessed by the parasite by placing leeches which had imbibed spirilla containing blood in a temperature of 0°C. for three to ten days ; after thawing the leeches, the spirillum was found still to possess vitality.

Dessication is rapidly fatal to the spirillum.

Electricity.—The effect of a weak electric shock is very rapidly fatal to the motion of the spirillum, motion thus lost is not again regained (Moczutkowsky ($_{p.\ 198}^{40}$).

Weigert, who first carefully investigated the effect of various substances, divided them into two main groups, namely—

1. Those in which after the death of the spirillum, the filaments are preserved for some time.

2. Those reagents which cause their complete and rapid disappearance.

Among those belonging to the first group are strong salt solution, urine, solution of bichromate

of potassium and carmine solution ; under their action the motion of the spirillum remains for a short while unchanged, then slows, and finally ceases leaving the filaments stretched out. The following substances leave the filaments in the spiral form : solution of carbolic acid, solution of permanganate of potassium, iodine solution (when not two diluted), and osmic acid $\frac{1}{2}$ per cent. solution.

In the second group, namely, those substances which cause total disappearance of the spirillum are glycerine (as previously pointed out by Obermeier [2]) caustic potash, distilled, and ordinary water. The action of caustic potash is exactly opposite to its effect on other bacteria.

·5 per cent. salt solution preserves the motion of the spirillum for a long time as first pointed out by Engel. Heydenreich went as far as to state that they retained their motion longer in this than in blood serum. Litten stated that salt solution produced a varicose condition of the filaments a statement which has not received confirmation.

Solution of bicarbonate of soda has only a slight influence on the spirillum (Engel, Obermeier). A solution of ·05 per cent. of iodide of potassium causes instant death. Salicylic acid ·1 per cent. does not affect motion, ·2 per cent. stops it. Creasote ·6 per cent. solution arrests motion.

The effect of a current of carbonic acid, or of oxygen, is fatal to the spirillum. Likewise the

spirillum perishes more rapidly when exposed to the air than when kept in a hermetically closed tube (Moczutkowsky); but the effect of drying is probably the chief cause of this.

Quinine, Engel $_{(p.\ 411)}^{3}$ showed did not affect motion when less than in 5 per cent. solution. Moczutkowsky gives 1 per cent. as the lowest concentration which influences motion; to produce this in the blood would require the administration of 30 grammes of quinine. Strychnia ·008 per cent. stops motion.

The admixture of any of the human secretions causes prompt cessation of motion.

Chapter IV.

Period in which the Spirillum is present.

Knowing as we do that the Spirillum Obermeieri is the cause of relapsing fever, we must expect the parasite to be present in every typical case of the disease; in fact, we might say, that "*if no spirillum is present the case is not one of relapsing fever.*" Many observers have recorded a few cases in which they failed to detect the parasite, though otherwise clinically agreeing with the disease; but the number of such instances has diminished as our methods have improved. It must be remembered, especially in the early stages of the disease, that the spirillum is only present in small numbers, and that because it is absent in one specimen, we should not conclude that it is not present in the blood; more than one specimen should be examined, and if even then it is not found, a preparation stained by one of the methods already given should be made before arriving at any conclusion. In outbreaks of relapsing fever, we often come across febrile attacks in which perhaps a distinct history is not obtainable; some of these are, no doubt, late relapses, whilst others may be abortive cases; in these spirilla are not often seen, but we invariably come across some of the structures mentioned in

Chapter VI, especially prominent, are the elongated dumb-bell shaped motile bodies.

Obermeier stated that the spirillum was absent during the apyrexial stage[1], and present from the first to the last day of pyrexia[2]; this statement has since received abundant confirmation, and it has generally been accepted. In 1888 Naunym [112] described a case in which in opposition to all previous observations, the spirillum was constantly found for 14 days, but their number during the apyretic period was very much smaller. Langovoi in 1894 [133] came to the conclusion that the spirillum never completely disappeared from the blood after the fall of temperature; but that it was found even in the apyretic stage but not in large numbers; this statement is not in accordance with the experience of any other observer with the exception of the single case recorded by Naunym.

Weigert in 1873 ($_{p.\ 589}^{5}$) first stated that the parasite was found in the blood with rising temperature, but it was not till the publication of Heydenreich's work that sufficient importance was attached thereto. Heydenreich laid down that the spirillum was present in the blood before the pyrexia, and was the cause of the pyrexia; he stated that he had found them to precede the rise of temperature by nearly 24 hours. Carter ($_{p.\ 355}^{76}$) in 12 cases specially treated in the incubation period of the first relapse found the spirillum 48 hours before the outset of pyrexia. As far as human beings are concerned, the opportunity of

observing the blood before the outset of the primary, or invasion attack, is not likely to arise; but if daily observations are made anterior to the occurrence of the first relapse, one can frequently convince oneself that the spirillum is present in the blood before the rise of temperature. I have not succeeded in finding a fully developed spirillum as much as 24 hours before a relapse; but I have often observed the parasite some hours before, and I have been able to warn the patients much to their surprise of an impending relapse.

Experimental inoculation in monkeys has almost invariably shown that, what occurs in man before the first relapse, is similarly seen in monkeys before the invasion attack; and there is no reason to doubt that the same takes place in man; but this should be borne in mind that in man whilst one can easily find the spirillum in the earlier period of the relapse one can easily miss them in the earlier period of the invasion attack as they are present in much scantier numbers. Once the spirillum has appeared, it increases numerically, until just before crisis when it completely disappears.

Moczutkowsky ($^{40}_{\text{p. }86}$) has given the following table as to the numbers of spirilla present on each day:—

10 hours	$\frac{1}{176}$	*
24 „	$\frac{1}{4}$	
48 „	2	
72 „	$4\frac{1}{2}$	
4th, 5th & 6th days and up to the day of crisis various between	$3\frac{3}{4}$ & $21\frac{1}{2}$	

after the temperature rises above 38°c

Spirilla per field.

* By this is meant 1 spirillum in 16 fields. L. J. P.

On the day of crisis—

16 hours	from the	commencement	of	sweating	12
8	„	„	„	„	$8\frac{1}{2}$
5	„	„	„	„	6
3	„	„	„	„	$5\frac{1}{4}$
2	„	„	„	„	$3\frac{1}{2}$
1	„	„	„	„	$3\frac{1}{2}$
$\frac{1}{2}$	„ after	„	„	„	no

Spirilla per field.

Moczutkowsky did not believe the parasite disappeared before crisis.

Though severe cases are sometimes seen with a comparatively small number of spirilla, the presence of a large number of parasites indicates severe infection. The amount of pyrexia present does not seem to bear any relation to the number of parasites present.

The following table shows a number of observations made by me, together with the average temperature taken at the time or just before the examination.

Spirilla.	Number of observations.	Average temperature.	Remarks.
Very few ...	25	101·8	Very few = 1 or 2 in whole specimen.
Few ...	24	101·7	Few = 1 or 2 p. field here and there.
Fairly numerous ...	42	102·3	Fairly numerous = 2 per field everywhere.
Numerous ...	35	102·1	Numerous 3 or 4 per field.
Teaming ...	19	102·2	Teaming 5, 6 or more per field.

The average of temperature in the two first instances is but slightly lower than in cases when the blood was teaming with spirilla, and would probably have been much closer had not the former included a large number of relapse cases in which the rise of temperature is more gradual. In individual cases an increase of the number of parasites was not attended by corresponding increase of temperature. Though therefore the height of the temperature curve does not depend on the number of spirilla, the appearance of the parasite causes a rise of temperature, its presence causes a continuance of pyrexia, and its disappearance is followed by a return to the normal.

The spirillum, as a general rule, disappears from the blood before the crisis; this statement first made by Engel has received abundant confirmation since. There are cases no doubt in which a few spirilla survive the crisis but these are exceptions. Bliesener [6] saw spirilla in small numbers one hour after the beginning of crisis. Obermeier saw a few spirilla in two cases after crisis. Birch Hirschfeld [12] observed them in the course the first twodays of apyrexia, Muellendorff ($_{p.\,633}^{39}$) on 2nd and 3rd day of apyrexia. Litten is mentioned by Weigert ($_{p.\,485}^{29}$) as having observed them in 2 cases after crisis. Riess ($_{p\,653}^{36}$) saw them in 12 cases after crisis, a large number as the cases observed by him were not many; Guttmann ($_{p.\,8}^{47}$) saw one spirillum in apyrexia

in 250 cases. Lachman ($_{p.\ 535}^{48}$) saw it only in one case. I have seen a single spirillum moving very slowly in two different cases after the crisis when the temperature was subnormal.

Litten, Unterberger, Heydenreich, Muellendorff, and many others have observed the spirillum in pseudo crisis, and several observers have seen them in cases where the temperature was intermittent, the spirillum being present both when the temperature was high and low. I saw one such case in which the temperature was quite intermittent in the first relapse. Metschnikoff has described a case in which the spirillum was present in a monkey whose temperature never rose above normal.

All elevations of temperature immediately after a true crisis, or in the earlier part of the apyretic period, *are not accompanied by the presence of the spirillum in the blood.*

The spirillum is found in much larger numbers in the first relapse than in the invasion attack. In the 2nd or 3rd relapses it is frequently not found in ordinary fresh preparations, but it is revealed by staining the specimen. I have often observed immature forms at these periods, but I failed to detect the spirillum in 3rd and 4th attacks in fresh preparations. Moczutkowsky found spirilla in a 4th relapse.

Nobody has hitherto succeeded in finding the parasite in any of the body secretions or excretions.

Engel failed to find it in urine, sweat, parotid secretion, saliva, and in vesicles after blistering. Moczutkowsky ($^{40}_{p.\,85}$) also failed to find them in pus, human milk, or fæces.

The earlier writers such as Ponfick and Orth believed that the spirillum could not be found in the blood of the dead. Heydenreich [26] first demonstrated its presence in the blood of a corpse 17 hours after death. Guttman ($^{47}_{p.\,8}$) saw motionless spirilla 36 hours after death; Albrecht observed spirilla in 15 cases even up to and over 40 hours after death. Carter and Lachmann likewise saw spirilla in the dead body. Albrecht believed that the spirillum could live for 12 hours after the death of the patient, and went as far as to state ($^{64}_{p.\,82}$) that the spirilla obtained from the dead body did not lose their form by drying, whilst fresh spirilla do.

Chapter V.

Changes produced in the blood by the Spirillum—Probable cause of its disappearance from the blood.

Of the chemical changes produced in the blood we know nothing. Most observers have been contented with saying, that there was an increase of fibrin, an increase of salts, and a diminution in the proportion of water. Although McCormack had many years ago pointed to the presence of an increased number of white cells it was not till 1875 that Laptschinsky [20] by enumerating the cells, in a case of relapsing fever brought the matter more prominently to notice. In 1874 Ponfick called attention to the number of large granular cells found in the splenic vein, and also stated that when the splenic enlargement is great, the cells are found not only in the splenic vein, but also in the general circulation. These cells vary between $\frac{1}{1200}$ to $\frac{1}{800}$ of an inch in diameter, they are more or less translucent and possess a large number of small granules. He also called attention to the co-existence of large endothelial cells derived from the walls of the blood vessels.

Soudakewitch and Nikiforoff have occasionally seen cells possessing a vesicular like nucleus.

Bockmann in 1881 [63] enumerated the red blood corpuscles in four cases, and came to the conclusion, that there was a diminution in numbers during the attack,

attaining its maximum after the crisis, and gradually approaching the normal during the apyretic stage.

We have thus in the blood of relapsing fever an increase of the white cells, including granular cells ; the presence of a large number of endothelial or hyaline cells derived from the vascular endothelium ; and according to Bockmann a diminution of the red blood corpuscles, but as to the latter point further observations are necessary.

The increase of white cells commences before crisis and diminishes gradually after it; in the majority of cases the increase is very marked, and it is generally more pronounced in the first relapse. My impression in the cases observed by me, was that the maximum increase was observable at crisis, or immediately after. Heydenreich stated that the proportion to the red cells became from $\frac{1}{80}$ to $\frac{1}{20}$ or even in one case $\frac{1}{9}$.

The observations of Laptschinsky and Heydenreich were made when our knowledge of the leucocytes was imperfect, and before the labours of Ehrlich had taught us how to differentiate the leucocytes according to their reaction towards the different aniline dyes. In 1893 Ouskow of St. Petersburg published a series of observations on 15 cases in which the various varieties of leucocytes were enumerated; as these constitute the only recorded enumerations hitherto published, it has been considered advisable to reproduce the chart given by him which gives a detail of his results (*vide* Plate II end of book).

Ouskow's observations indicate that the leucocytes increase during the paroxysm, and that they diminish after, or immediately before, the crisis. The increase was chiefly in the polynuclear elements ; the most characteristic point, according to Ouskow, is the reversal of the proportion between the early forms (lymphocytes) and that of the mature elements ; during the attack both were present in almost equal numbers, the small lymphocytes sometimes being even in larger numbers. After crisis there is not only a diminution in the total number of colourless cells, but a change in the proportion of the different varieties. The mature elements (mononuclear cells) fall to about 60 per cent. of the total, while the number of small lymphocytes exceeded, sometimes 15 times, the large mononuclear elements. The increase in the number of large mononuclear elements, Ouskow attributes to the changes induced in the spleen in which organ probably the small lymphocytes are transformed into large mononuclear elements, and thence pass into the blood. The increase in the number of small lymphocytes he explains by the hyperæmia and hyperplasia found in the lymphatic glandular apparatus in pretty nearly every part of the body, especially the extra peritoneal glands.

The classification of leucocytes used by Ouskow differs from that given by most authors. As it may be of use to those intending to enumerate the

leucocytes a short account of the varieties is given. An excellent paper by Kanthack and Hardy* may be consulted if further information is desired.

Ehrlich described five forms of granulation cells, namely :—

1. *Eosinophile*, with coarse and large granules, staining deeply with acid aniline dyes.

2. *Amphophile*, with fine granules, staining with both acid and basic dyes.

3. *Basophile*, large, coarse granular cells, staining only with basic dyes.

4. *Fine Basophile*, with very fine granules, mononuclear staining with basic dyes.

5. *Neutrophile*, polynuclear, staining with neutral dyes only.

Kanthack and Hardy have shown that Ehrlich's neutral stain is really an acid dye, and have adopted the following classification, which I have arranged in a tabular form.

Name of cell.	Reaction.	Nucleus.	Where found.	Whether phagocytic or not.
Coarsely granular..	Oxyphile	Large horse-shoe shaped.	Abundant in cælomic fluid, in serous cavities, in interstices of connective tissue. In blood constitutes 2-4 per cent of leucocytes.	Not.
Finely granular ..	Faint ,,	Branching or Polymerous.	Absent in cælomic fluid. In blood constitutes 20-70 per cent of leucocytes.	Phagocytic.
Coarsely ,, ..	Basophile	Round ..	Found in cælomic fluid absent from blood in health.	Not.
Finely ,, ..	,,	Tri-lobed ..	In blood 1 to 5 per cent. of leucocytes	Not.
Hyaline cell ..	....	Round or kidney shaped.	Abundant in cælomic fluid. In blood 2 per cent. of leucocytes.	Phagocytic.
Lymphocyte ..	....	Round ..	In blood constitutes 30 per cent. of leucocytes.	Not.

* Journal of Physiology, XV, 1894, p. 81.

The coarsely granular oxyphile corresponds to Ehrlich's					Eosinophile.
„ Finely	„	„	„	„	Neutrophile and Amphophile.
„ Coarsely	„	basophile	„	„	Basophile.
„ Finely	„	„	„	„	Fine Basophile.

The question as to why the spirillum disappears before, or at crisis, has been one which has engaged the attention of all observers. Obermeier was content with stating the fact that the parasite was present during the pyrexial period and absent during the apyretic stage. Since 1873 a number of theories have been evolved to explain its disappearance.

1. *The high temperature theory* of Heydenreich (1876-1879).—As the result of his experiments on the effect of temperature, Heydenreich stated that the rise of this to 40°C. just before crisis was the cause of the disappearance of the filaments. This theory which for a long time held the ground does not admit of proof for the following reason:—

(*a*) It has been experimentally proved by Paternatzki, that the spirillum can withstand even a temperature of 45° for $\frac{1}{2}$ hour; Moczutkowsky has found a temperature of 48°C. necessary for its destruction. Cases have been recorded with a temperature of 42·5C. in which the spirillum was not affected.*

(*b*) The parasite frequently disappears without the temperature ever reaching 40°C. and in monkeys it has been known to disappear even with normal temperature ($_{\text{p. } 189}^{104}$).

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* Obermeier, Virchow's Archiv., Bd. 47.

(*c*) The lowering of temperature in defervescence by lysis does not stop the disappearance of the spirillum ; these continue to disappear even with the lower temperature. Alexander some years ago pointed out that antipyretics by lowering the temperature produced an increase in the number of spirilla. Antonoff [102] has more recently made the same statement. I have never observed such increase after the administration of either antipyrin or antifebrin, nor have I seen any decrease in cases where the temperature was intermittent.

It is probable, however, that a high temperature may exert an injurious influence on the growth of the parasite, but there is no doubt that there are other causes at work which lead to its total disappearance.

2. *Thickening of the blood theory*, Moczutkowsky (1879).—This observer, though evidently believing that there was a diminution in numbers before crisis, claimed that the final disappearance of the organism was due to the thickening of the blood produced by the profuse sweating at crisis, and sometimes by the diarrhœa then present. To prove this he mixed outside the body spirillar blood with glycerine, sugar, white of egg and saliva, forgetting that these substances would cause the death of the spirillum irrespective of their thickening effects. Moczutkowsky also produced perspiration by means of jaborandi and wet packing,

and claimed that the thickening of the blood thus produced was injurious to the spirillum. The fact that the disappearance of the spirillum is so generally anterior to the crisis disposes of this theory.

3. *Albrecht's theory* (1883)—Albrecht propounded the theory that the spirillum disappeared from the injurious effects of its own products as follows: "As the spirilla increased in numbers with the progress of the disease, so likewise the products (toxins) generated by their increase, until at last the quantity circulating in the blood is sufficient to kill the microbes and the access ceases. After five to eight days the germs which have resisted the action of the poison reach their full development into spirilla; the blood without doubt still contains some poison from the spirilla of the first attack, it will therefore become saturated more quickly by the second generation, and this prompt saturation accounts for the shortness of the second and likewise of the subsequent attacks."

Ingenious as this theory is it is not supported by facts. We know nothing about the products generated by the spirillum, but all observations point to their not being injurious to its own life. In the system, Albrecht states there is a constant elimination of this supposed poison, but no such elimination can go on in a glass tube. It is a well-known fact, however, that while spirilla taken from a given case will live for days in a glass tube, the blood of the

patient from which the specimen was obtained will soon cease to possess the parasite.

4. *The spirillum breaks up having reached maturity.*—Hanau* has stated that the periodicity of relapsing fever was due to developmental phases in the life of the spirillum. Mulhausser [87] that the cause of its breaking up was its age.

This is a theory which at first sight appears a probable one but which does not bear investigation. Whilst the first attack of the disease generally lasts six to seven days, we know that the subsequent relapses are of much shorter duration. As has already been stated, spirilla contained in glass tubes live longer than those in the blood and show no signs of reaching maturity. In these cases no sign of periodicity is observable, the spirilla disappearing at variable periods.

5. *Metschnikoff's phagocytic theory* [104].—Ponfick ($_{p.\,163}^{14}$) judging from the analogy of the behaviour of particles of cinnabar when introduced into the blood, was inclined to the belief that in relapsing fever the spirillum probably likewise passed into the splenic pulp cells ; but he was not able to prove this from deficiency in the methods of staining at that time. Birch Hirschfeld and Lubimoff saw spirilla in the malpighian corpuscles, but these were not enclosed within cells. Metschnikoff's

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* Zeitschrift f. Klin. Med., Bd. XIII, p. 3.

phagocytic theory is founded on the following experiments:—

Commencement of illness.

1. A monkey was inoculated and killed as soon as spirilla were visible in the blood (59 hours after). The splenic juice contained no spirilla, either between or within the cells. The spirilla were exclusively found in the blood.

Fully developed disease.

2. A monkey had a portion of the spleen removed by the thermo cautery on the second day of the attack with a temperature of 42°C. Spirilla numerous in the blood. Spirilla were then found, some between the splenic cells free, others even were within lobed leucocytes, neither the small lymphocytes of the malpighian corpuscles nor the large pulp cells had any spirilla.

Fully developed disease just before crisis, with no spirilla.

3. A monkey which had been twice infected was killed just before the crisis, the temperature being 41·5°C., but the spirilla having already disappeared from the blood. The blood of the various organs contained no spirilla. By means of sections it was found that the spirilla were exclusively found in the spleen, here they lay partly enclosed within the leucocytes (with lobed nuclei), and some times free between the cell elements. The enclosed spirilla were some faintly, some intensely stained. The lymphocytes and the splenic macrophages contained no spirilla.

The above experiments showed that the spirilla collected in the spleen at crisis.

Apyretic stage just after crisis.

4. Monkey killed after crisis. No spirilla in the blood of the spleen, liver or medulla. Preparations stained showed large numbers in the spleen, free spirilla extraordinarily few, and these he thought might have been set free from the cells during the preparation, the majority were contained within lobed leucocytes, the lymphocytes and splenic pulp cells contained none. Sections of all other organs showed absence of spirilla. An emulsion of this animal's spleen produced the disease in another monkey, thus showing that the spirilla in the spleen were still virulent.

Apyretic stage some time after crisis.

5. The monkey of experiment 2 died one and a half days after the crisis. Spirilla found exclusively in leucocytes, but in small numbers compared with those which had existed in the blood during life. Individual spirilla stained well, but a large number were very faint thereby indicating their decay, so much so that they might easily escape observation.

Metschnikoff's theory therefore is that at crisis the spirilla disappear from the blood and collect in the spleen and in no other organ, and that the spirilla whilst possessing full activity penetrate within the lobed leucocytes where they are destroyed. The relapse in human beings he explains by

saying that the leucocytes are not able to devour all the spirilla, that those that are left free between the cells give rise to a fresh generation. Metschnikoff did not observe at any time any signs of phagocytosis in the blood.

In 1891 Soudakewitch, a disciple of Metschnikoff's, undertook some further researches in order to discover the fate of the spirillum in normal and spleenless monkeys. He performed three experiments in normal monkeys which he states gave the same result as in Metschnikoff's cases, but he found some appearances which are of considerable importance. In the blood of the vena cava of a monkey killed on the second day of the disease, he saw 10—15 leucocytes containing spirilla, the number of these contained varied between 1, 3 and 6, sometimes isolated, sometimes in a small heap. Some undulated, others straight, with interruptions in the course of the length of the thread dividing into two or three portions (*vide* Plate III at end of book).

At the end of some threads, and sometimes also in their midst, he observed deeply stained granulations. In some cells the granulations lay separate in the protoplasm of the cell or collected in small groups. He did not find this condition in man. I have myself seen what appeared to be spirilla contained within large masses of protoplasm in several cases in the blood of man just after the crisis; the spirilla were coiled up generally straight

not undulated, but I never saw in them the granulations observed by Soudakewitch. Carter, as is known, at one time believed that the spirilla were developed within cells, no doubt from the fact that he had observed these within their interior. In page 344 Carter says, "some granule cells were quite peculiar in that the granules were bright uniform and active, and clearly were not fat, they radiated round a central nucleus or were disposed in wavy spiral or reticulated lines as if prefiguring some filament within," and in page 365 he observes, "large cellular plasmoid masses containing granules, and filaments are to be seen in infected blood, very numerous in splenic venous blood of the monkey; and my first conviction was that this evidence sufficiently demonstrated the real mode and place of parasitic reproduction. It was supposed that the free germs in the form of granules liberated in the plasma were like other foreign particles taken up by the white cells and endothelium, multiply and grow, and at definite periods become free and dispersed by "rupture of the cells." Carter though wrong as to the mode of reproduction of the spirilla, as he himself admitted subsequently, plainly saw what Soudakewitch observed many years after.

Soudakewitch, by the removal of the spleen in two monkeys, 24 and 20 days respectively before inoculation, claims to have shown that the monkeys

possessing no spleen were unable to carry on a combat against the spirilla, the spirilla multiplying enormously and causing the death of the animals. It may be remarked that one of the two monkeys had a severe traumatic inflammation of the parietal region, and the other a localised purulent peritonitis.

Schwalowski [121] has also made an experiment in a spleenless monkey which proved fatal.

Having considered the evidence offered by Metschnikoff and Soudakewitch, and assuming for the present that the theory of phagocytosis in general is correct, one cannot help thinking that Metschnikoff's theory is not one that can be accepted. As Weigert [106] pointed out some years ago, it is difficult to explain why the parasite, when first introduced into the body and is present in small numbers, is not taken up by the phagocytes, or why, it is not taken up by the leucocytes during the pyrexial stage. If the spleen leucocytes have phagocytic properties what inhibits their power during the febrile period? To this one may add that Metschnikoff has not explained what peculiar attractive action draws all the spirilla to the spleen within a few hours there to undergo destruction.

Tictin [127 & 134] has more recently made some experiments which prove that a monkey whose spleen has been removed can live even after repeated

inoculation. Briefly his experiments were as follows :

Experiment I.—Monkey died. Death from acute tuberculosis.

Experiment II.—Monkey inoculated one month after excision of the spleen; no infection, two weeks later again inoculated, and shortly after inoculated for the third time without effect, *thus in spite of three inoculations and the absence of the spleen the animal remained immune.*

Experiment III.—A monkey after having had an attack of relapsing fever had its spleen removed one month after infection. When it had recovered from the operation, it was inoculated and had a fresh attack lasting three days from which it completely recovered. *The absence of the spleen did not therefore prove an impediment to recovery.* This monkey had several further inoculations, one month after, then two weeks, and for a third time three weeks later to which it proved immune.

Experiment IV.—A monkey after removal of the spleen was inoculated, and had an attack terminating on 5th day. After a day it was again re-inoculated, the attack lasting two days; *the second attack was less severe than the first;* four days after recovery it was inoculated for the third time. This animal died from cardiac paralysis from œdema and fatty degeneration. The parasites twice disappeared in spite of the absence of the spleen.

Tictin arrived at the following conclusions:—

1. Monkeys inoculated with spirillar blood recover from the attacks of recurrent fever without the influence of the spleen.

2. Not only did they recover but they showed an immunity towards the disease.

3. Spleenless monkeys got over the attack with more difficulty than normal monkeys.

4. In the blood of spleenless monkeys one finds neither during the attack nor after it any appearance of phagocytosis.

5. Monkeys which are immune to subcutaneous injection of spirillar blood remain likewise immune to such injection even after removal of the spleen.

We have considered in turn the various theories hitherto brought forward to explain the disappearance of the spirillum from the blood, and we have found that one and all do not bear investigation.

We are not aware what the duration of life of the spirillum is, and whether one or more generations are evolved in each attack; but we know that the first attack is the most prolonged and that each subsequent relapse gradually diminishes in duration. We also know, as it has been repeatedly proved, that if blood containing the spirillum is placed in a hermetically sealed tube, or is imbibed by a leech which is subsequently frozen, the spirillum will be found alive for a variable time, whilst the blood of the patient will soon cease to show them. There

must therefore be something in the blood of the patient which exerts an injurious influence, a something which does not exist in sufficient quality in the blood contained in the glass tube ; but which exists towards the end of the attack, for as we have seen in page 18 the spirillum shows sign of approaching death as indicated by the slowness of its motion.

We have already seen how in relapsing fever there is a considerable increase of the white cellular elements of the blood, a leucocytosis, which only begins to diminish after the disappearance of the parasite from the blood. Now, we must ask ourselves is this leucocytosis a purposeless condition generated in the body, or is it evolved to serve some purpose ?

During the last few years chiefly as the result of the labours of Buchner and others a considerable amount of attention has been devoted to the germicidal properties possessed by the blood. Buchner considered that the leucocytes possessed germicidal properties ; Emmerich and others proved that this property was possessed by the alkaline blood serum. Hankin in 1893 showed that though this germicidal substance was present in the cell free serum, it was derived from certain leucocytes. Ehrlich's eosinphile cells — the eosinophile granules he believed became dissolved in the blood serum, and thus gave rise to what he termed " defensive proteids."

V. Vaughan* has more recently found that the bactericidal substance possessed by blood serum is either nuclein or some substance intimately associated with it, the presence of nuclein thus indicates its origin from the nucleated cells. Kossel† has more recently confirmed Vaughan's work, but is inclined to believe that the germicidal substance is probably nucleinic acid. Kanthack and Hardy‡ have described the actual changes which take place when bacilli come in contact with the coarsely granular oxyphile cells (eosinophiles) as follows :—

The coarsely granular oxyphile cells are strongly attracted to the bacilli ; after moving towards them they become applied to their surface; a quick streaming movement appears in the protoplasm and the eosinophile granules are discharged, after which the bacilli begin to show signs of degeneration. The hyaline cells, the phagocytes proper, remain quiescent, and are not even attracted towards the bacilli at first; but subsequently undergo proliferation and approach the masses of oxyphile cells surrounding the bacilli, fusing with them and forming a plasmodium. After this the oxyphile cells wander away leaving the hyaline cells containing remnants of bacilli within vacuoles. These observations were made with lymph. According to Kanthack and

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* Med. News (New York), Dec. 1893.

† Zeitschr f. Hygiene, XVI of 1894.

‡ Proc. Royal Society, 1892.

Hardy the hyaline cells are the phagocytes of the lymphatic and cælomic system ; the finely granular (neutro and amphophile) are the hæmal phagocytes; while the coarsely granular oxyphile cells (eosinophile) possess excretory functions.

If we turn to Ouskow's table we shall see that there is not only an increase in the total number of leucocytes, but the largest increase is in the polynuclear elements which, according to Ouskow ($^{131}_{p.\ 89}$) may even amount to 82 per cent. of the total number of leucocytes. It is impossible to find the actual increase of the eosinophile (coarsely granular oxyphile) cells because Ouskow includes these with the neutrophile (finely granular oxyphile) under the heading "polynuclear," but there appears to be no doubt that they are increased, as coarsely granular cells have been frequently described as present in the blood of relapsing fever. The increase of polynuclear elements is found all through the attack, the maximum being reached on the day of crisis. The leucocytosis gradually diminishes after the crisis and by the date of the first relapse is scarcely perceptible, the re-appearance of the spirilla generally in greater numbers than in the invasion attack causes a fresh and more abundant leucocytosis, and the spirilla disappear from the blood in a shorter period than in the first attack.

Carter (p. 342) observed that in the relapse the white cells were more abundant than in the

first attack, and he also p. 344 makes this remark: "In milder instances of spirillum fever, I noted that when white cell production was copious, these large (granule) cells co-existing then the spirillum was either absent or scanty, this fact seems to indicate a substitution or at least an incompatibility of leucocytic and parasitic production." These observations made long before the abovementioned properties of the leucocytes were known are of considerable importance.

The leucocytosis in relapsing fever is not without analogy in other infectious diseases. For example, Kanthack and Sevestre have pointed out that a high leucocytosis in scarlatina indicated a pronounced reaction against a severe infection, a slight leucocytosis a mild infection; Kanthack and Lloyd have also shown that well marked leucocytosis in diphtheria indicates a good reaction, a low leucocytosis accompanying most if not all fatal cases.* Limbeck† and Billings‡ have also pointed out the favourable effect of leucocytosis in pneumonia. Von Limbeck says that in the majority of cases there is a more or less considerable inflammatory leucocytosis, that is, increase of the multinuclear or neutrophile, or finally granular eosinophile cells. A good leucocytosis indicates a good reaction,

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* Article on Diphtheria Albutt's system of Medicine, Vol. I, p. 730.

† Grundriss einer Klinische Pathologie des Blutes. Fischer-Jena.

‡ John Hopkins Bulletin, v. 43.

absence of leucocytosis is often if not always a bad prognostic sign. Billings, in speaking of pneumonia, says marked leucocytosis is favourable, complete and continuous absence of leucocytosis unfavourable. Sternberg* says, "it has been shown by various investigators that the number of leucocytes increase in various diseases, and this together with the increased alkalinity of the blood appears to be a provision of nature for overcoming the infection which has already occurred," and in page 31 he observes : "Experimental evidence leads us to the conclusion that natural immunity is due to a germicidal action in the blood serum which has its origin (chiefly at least) in the leucocytes, and is soluble in an alkaline medium * * * * also that general infection at least in some infectious diseases is resisted, and in non-fatal cases overcome by an increase in the number of leucocytes and in the alkalinity of the blood serum which favours solution of the germicidal proteids contained in the polynuclear elements."

If a germicidal substance is produced in the blood, we would expect that a certain amount of immunity would be produced after a fully developed attack with one or more relapses. It is generally agreed that individuals though subject to be again infected *as a rule do not experience a*

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* Immunity and Serum Therapy, 1895, p. 3.

fresh attack for some time after, even though they may continue in the meantime exposed to the infection. Welsch, Warden and Mackenzie stated that second attacks followed one month after termination of the first. Berstein of Odessa, saw two attacks during two to three months. Litten in 1872-73 saw five cases in which re-infection was between 29 days and four months after the first attack. O. Motschutkowsky has recorded cases in which a fresh infection appears to have supervened on the previous attack. These all must be considered to be exceptional cases which have been thought worthy of record.

If we look to experimental evidence we find that the only inoculation experiment carried out in man by J. Moczutkowsky ten weeks after the last (4th) attack proved unsuccessful. Carter carried out two re-inoculation experiments in monkeys, in one the first attack was very slight lasting only 12 hours, whilst after re-inoculation the pyrexia lasted 66 hours. The second case had also a slight original attack of 27 hours, the animal was killed soon after the second attack commenced so its duration could not be ascertained. These two monkeys had very slight primary attacks.

Koch carried out also two re-inoculation experiments, one monkey had a typical attack, and, when inoculated again $8\frac{1}{2}$ weeks after the termination of the first, had a second attack. In the second case,

the first attack was represented by a slight elevation of temperature *with no spirilla;* inoculated five days after it had a short spirillar attack. It was again re-inoculated when the temperature reached the normal, producing a spirillar attack lasting one day.

Metschnikoff ($^{104}_{p.\ 179}$) performed three re-inoculations, in one the first attack lasted about 36 hours, the second was only transitory, the spirilla being only visible for an hour. He also mentions that in two other cases the result was somewhat similar.

Soudakewitch re-inoculated two monkeys. In one the first illness was not appreciable. The second had two attacks, the first lasting four, the second two days.

Tictin ($^{134}_{p.\ 842}$) experimented on a monkey which had an attack lasting three days; two weeks later again re-inoculated without success; after a short while inoculated for a third time and had a short attack lasting 24 hours.

Clinical and experimental evidence thus points to some protective influence produced by an attack, but this protection does not seem to be of long duration.

If we assume that the disappearance of the spirillum is due to the generation of some germicidal substance in the body, we must explain the enclosure of the parasite within the cellular elements of the spleen as not taking place during its life, but after its death or when it is approaching death. That the spleen should be the most frequent place for the ingestion of the spirilla is not to be

wondered at when we consider the conditions which exist in this organ. In a normal spleen, as we know, the blood cells move less readily through the reticulum than the plasma, and hence a concentration of corpuscles as compared with the blood plasma takes place within its meshes, at the same time the circulation is very slow. This slowing of the blood is much aggravated by the general enlargement of the organ and the changes in the vascular endothelium which are found in the recurrent spleen, and thus the spirilla will be in more close contact with the aggregated cells, and in their dying or dead condition will be easily taken up by the leucocytes.

In man probably rhythmic contraction of the splenic does not exist owing to the scantiness of the muscular elements ; but it is probable that by the diminution in size of the spleen which commences with the cessation of pyrexia many of the cellular elements including those enclosing spirilla may be squeezed out into the blood, and thus explain the appearances observed by me and apparently by Carter also in human blood.

Chapter VI.

What becomes of the Spirillum during the Apyretic stage?

This question is one which must for the present be considered *sub judice*, and which will probably remain unanswered until the parasite is artificially cultivated.

It will be convenient to discuss the subject under the following headings:—

Firstly—Does the spirillum at the crisis break up and give rise to germs which circulate in the blood till they finally develop into the fully grown organism?

Secondly—Does the spirillum collect in any part of the body subsequently to be set free and thus produce a second attack.

Thirdly—Does the spirillum continue during the whole of the apyretic stage but in diminished numbers?

Does the spirillum break up at crisis giving rise to a fresh lot of germs?—Though Metschnikoff has stated that the spirillum retains up to the end its full vitality, on the other hand, most observers are agreed (page 18) that just before crisis it shows signs of impending death as indicated by its diminished vitality. After crisis too the conditions observed are such as to show that there has been a breaking

up of the spirillum, and that other structures are then present which are probably the precursors of the parasite. At the present time one serious objection to this assumption is that all attempts to reproduce the disease with non-spirillar blood have hitherto failed.

As to the presence in the blood of structures which are probably the precursors of the spirillum we have a considerable number of observations:—

Engel in 1873 ($_{p.410}^{3}$) found extraordinarily fine dots, often apparently joined by a short thread with active motion.

Nedsvetzki [9] called attention to the presence of small round cells visible by magnifying 900—1000 diameters. These had independent motion in their own axis, or upwards or downwards or even sideways, he called them *hæmococci* and believed them to arise from the breaking of the white corpuscles.

Bliesener [6] found fine strongly refracting granules single, or in pairs, the latter united by a fine short thread so that it looked dumb-bell shaped, these structures possessed a quivering and slow progressive motion.

Bettelheim described large punctiform bodies, small punctiform bodies and rod like structures half the size of a blood cell.

Heydenreich [31] described dots with such rapid molecular movement that it appears as if they moved capriciously more or less by means of an imperceptible thread. He believed them to be spores.

Muellendorff ($^{39}_{p.\ 63}$) says in the plasma are found bright brownish grains which appear to possess a motion of their own. They are seen within the leucocytes.

Guttmann ($^{47}_{p.\ 3}$) says of these structures that their size varies between $\frac{1}{30}$ and $\frac{1}{20}$ the size of a red corpuscle, sometimes quite round, sometimes a little oval, at times faint, at times bright with a red lustre mostly single, sometimes joined so as to give a dumb-bell form, sometimes the connecting portion was not visible, at other times the connection was produced by a quite short filament. Once he saw three joined with one another. The motion was of a quivering kind, but at times very rapid passing quickly across the field. He believed these structures to be parasitic, and though he had seen them in other diseases in none in such numbers as in relapsing fever.

Albrecht [64] describes minute corpuscles resembling dots, not ascertainable whether round, oval or angular, generally in constant movement quivering or progressive. Double such punctiform cells resembling dumb-bells joined by a faint connecting substance. The interval between one corpuscle and another is approximately either one or two diameters of a corpuscle. The movement is distinct sometimes one way or another, sometimes rotating. He also described rosary like structures with three or four or more dots. In 1880 [45] Albrecht

had already described the development of such structures into spirilla under the cover-glass, and in 1881 ($^{64}_{p.\ 106}$) he gave seven cases in which the blood taken from the apyrexial period and containing no spirillum developed it after the course of two or three days. The details of some of the cases given by him are certainly not very convincing.

Lachmann ($^{48}_{p.\ 541}$) claims to have developed the spirilla in three cases in which the blood was taken at the commencement of the relapse.

Carter ($^{76}_{p.\ 328}$) says: "In the interval active specks are found with molecular movement, it seemed as if the molecules were growing up to spirilla; the spirilla were always scanty at first being preceded by particles capable of being regarded as initial or immature forms." In page 346 "free granules, specks or short rods found in 21 per cent. of observations in pyrexia of first attack, less often at acme, but in 80 per cent. at the fall * * * * I particularly noticed that the rods were most plentiful in specimens kept for hours * * *; on the other hand, there was the striking fact that these free particles were much oftenest seen at the critical defervescence." In page 347 he mentions some cases in which he saw some immature forms, and one case where "with active spirilla there existed others beaded or nodulated as if undergoing development or giving off spores." He also mentions that these bodies (granules and rods)

"originated from minute specks and extension proceeded by budding alone or combined with elongation of the growing rod, a smooth filament might result wavy or spiral and active or quiescent* * *. The fact of their appearing oftenest at the close of the febrile attack and with the disappearance of the parasite indicates a special connection."

Sarnow [74] has noticed the presence of small refractive bodies during apyrexia.

Mulhausser ($_{p.}{}^{87}_{101}$) who has investigated various spirilla calls attention to the prevalence of small forms, and goes as far as to say that the *bacterium termo* is the commencement of the recurrent spirillum, and in page 113 he says, "the spirillum lengthens and breaks up thus laying the seeds for new spirilla."

Jaksch * ($_{p.}{}^{88}_{186}$) mentions having seen a number of diplococci-like bodies especially some hours before the attack, and he believes that these grow into thick rods and from these the spirillum develops.

Krause ($_{p.\ 6}^{99}$) has observed both single and dumb-bell shaped motile bodies.

Paternatzki [120] mentions the presence of these motile bodies, and that they are capable of resisting a higher temperature than the spirillum (65°C) ; he also believes that the spirillum becomes replaced by chain-like beaded structures.

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* Jaksch's Clinical Diagnosis, English translation, p. 30.

Karlinski [123a] has described the presence of curved rods and small thick spirilla which he claims to have developed into fully grown parasites within capillary tubes and within leeches

Soudakewitch [123] as already stated in page 47 has seen in the course and at the ends of some spirilla rounded granulations: these granulations in some instances were seen free, or in groups, within cellular elements.

In the cases observed by me, I invariably found the structures described by some of the abovementioned authors. Although present in small numbers during the pyrexial period, they were found chiefly in the non-febrile stage especially immediately after the crisis. These structures sometimes appeared to be round, sometimes comma-like. In some cases they looked like diplococci; they were motile, the motion being of a quivering and rotating character. Transition forms between the diplococci-like bodies and the fully formed spirillum were not unusually seen ; for example, straight rods with knobbed ends, similar rods with knobbed ends but with one or more dots in their course, all these structures were motile moving either forwards or backwards. On one or two occasions I saw a distinct fine filament connected with some of the rounded or comma-like bodies, but I could not discern them in every case ; the impression given on viewing these structures is that their motion is produced by the presence of a

flagellum. I have on one or two occasions seen what appeared to be an encapsuled rod. The knobbed rod-like forms I have very often seen in the later relapses, but they occur at various periods before the freely developed spirillum is present.

When I first observed the rounded particles in the course of the spirillum (*vide* page 14) I was inclined to believe that the effect was purely optical. When I observed the rounded active particles so constantly and also frequently straight rods with similar rounded particles either at the extremities or in their course, I was struck with the similarity in size of these rounded structures, and my present belief is, as other observers have previously believed, that these rounded particles are the precursors of the spirillum.

Paternatzki [120] has shown experimentally that the rounded motile bodies can withstand a very much higher temperature than the spirillum; according to him whilst the spirillum perishes at a temperature of 45°C, the rounded bodies can resist a temperature of 65°C. It is possible that any germicidal substances which may exist in the blood though sufficient to destroy a fully developed spirillum may not destroy their germs; and these finally attaining their full growth will cause a relapse.

It must be mentioned that Baumgartnen and Metschnikoff and others have not found the above-mentioned structures, and are inclined to believe

that the spirillum multiplies by division. Nikiforoff believes the granulations found by Soudakewitch to be chromatin granules.

Does the parasite collect in any part of the body during the apyrexia being subsequently set free and producing a relapse?

This is Metschnikoff's theory which has already been dealt with in a previous chapter. According to this observer, the parasites which have not been destroyed by the splenic phagocytes remain between the splenic cells, subsequently undergoing division and being set free in the blood current give rise to a fresh attack.

Does the spirillum continue during the whole of the apyretic stage?

Langovoi [133] has stated that the spirillum multiplies by fission, and that it can be found in the blood in small numbers all through the apyretic stage. His observations have not received confirmation. The only other observer who has seen the parasite all through the apyrexia is Naunym who saw it only in one case.

Chapter VII.

The mode of entry of the Spirillum into the body.

Before considering the pathological changes produced by the spirillum, we must consider the possible mode of entrance of the parasite into the body. The *Spirillum Obermeiri* has never been detected outside the body, and as has already been stated it is absent from all the body secretions or excretions. Baumgartnen has suggested ($^{122}_{p.\ 845}$) that the parasite may possibly by its boring motion, pass out of the body, but this is hardly possible. There are other likely sources by which the spirillum can escape from the body, namely, the frequent hæmorrhages which occur in the course of relapsing fever. Epistaxis, blood tinged expectoration, and hæmorrhage from the kidneys or bowels, occurring during the attack or relapses would thus allow an egress of the parasite. In the same way the normal menstrual flow [Moczutkowsky ($^{40}_{p.\ 85}$)] will allow the parasite to pass out.

Another possible mode of propagation is by blood sucking insects such as mosquitoes, bugs, or fleas.

The spirillum will immediately break up if placed in water, or if dried, and thus it is likely that it will soon break up after leaving the body. The tenacity with which infection clings to buildings would be

best explained by the presence of spores, the formation of which at present remains a doubtful question.

Granted that the infective material is found outside the organism, it remains to consider the possible mode of entrance into the body

Entrance through the skin.—Irrespective of the propagation of the disease by experimental inoculation, cases have been brought forward in which the disease has been believed to have been introduced through scratches or wounds inflicted in carrying out *post-mortem* examinations in the bodies of relapsing fever cases. Carter ($_{p.\,403}^{76}$) mentions six cases, Lachmann ($_{p.\,531}^{48}$) one case, Schmidt two cases, and similar observations were made by Albrecht in the St. Petersburgh Epidemic, but in all these cases the possibility of other modes of infection cannot be excluded as they were medical men or subordinates. Though we have therefore no absolutely reliable case on record, the possibility of this mode of infection is not to be doubted.

Entrance through the alimentary canal.—The spirillum would, in the absence of spores, rapidly break up by the admixture of fluid and acid in the stomach.

Entrance through the lungs.—Is not a common channel of infection in the absence of spores, whether the spirillum could be inhaled, and thus cause infection, seems unlikely.

The mode of entrance of the infective organism of relapsing fever still remains unsolved, but everything points to the probable existence of spores as the medium of infection.

Chapter VIII.

General Remarks—The preparation of tissues for cutting sections, and the method of staining them.

Relapsing Fever being an infective blood disease, not only do we find the influence of the infection widely distributed, but as is to be expected the vascular structures such as the spleen, liver, and bone marrow are mostly affected. The changes in the endothelium of the blood vessels, and the consequences arising therefrom, together with the hyperplasia of the lymphoid structures in various parts of the body must be considered to be the most important pathological changes produced by the spirillum.

For many years it was considered that there were no pathological changes characteristic of this disease, and even now most text-books make but scanty allusion to it. The labours of Küttner, Ponfick, Lubimoff, and more recently of Puskhareff, Nikiforoff and others have placed the pathology of the disease in a more satisfactory basis. Though we may find many changes such as granular and fatty degeneration of the muscular structures and engorgement of the organs in many other infective diseases, the changes found in the spleen are so characteristic as to be almost distinctive of the disease.

The frequency of hæmorrhage in relapsing fever is easily explained by the changes found in the

blood vessels, as these will be dealt with in detail in considering the changes found in the spleen, there is no need for further describing them here: but it must be remembered that the changes are not limited to the vessels of the spleen, but are distributed throughout the whole vascular system. The pains in the muscles so frequently present in this disease are probably due to blocking of the small blood vessels. From a similar cause gangrene of the extremities, of the nose, lips, ears or cheeks have been known to occur.

In relapsing fever the symptoms only last during the pyrexial stage, that is, the period when the spirillum is present in the blood. We have no precise information as to how the pyrexia or the pathological changes are produced. From analogy we must believe that some toxic substance is produced, but such substance should exist in largest quantity just before crisis when the parasite is most numerous. As all the symptoms cease with the crisis and with the disappearance of the spirillum, it is evident that any toxic substance which may exist must very rapidly disappear from the system.

Whether the spirillum itself, irrespective of any toxine that it may produce, can mechanically cause changes in the delicate vascular endothelium, and in other cellular structures, and thus produce the symptoms of the disease is a matter which requires elucidation.

The great emaciation found in the disease is partly due to the high temperature, but to a greater extent probably owing to the alteration in the constitution of the blood.

The spirillum may be detected in tissues by squeezing some of the juice out, and staining it by one of the methods already described. It was in this manner that Lubimoff ($^{86}_{p.\,181}$) first succeeded in detecting the spirillum in the malpighian corpuscles.

It is necessary to obtain the organs soon after death as the parasite soon breaks up and disappears; the spirillum should only be looked for in cases dying during the first attack or a relapse.

Hardening tissues.—Alcohol is not a favourable medium as it destroys the spirillum. Fleming's solution may be used (Soudakewitch); but Müller's fluid has been found to be the most useful, the portions of tissue being subsequently transferred into alcohol. Nikiforoff ($^{124}_{p.\,212}$) has recently recommended a modification of Foà's solution as follows: Mix equal portions of a 5 per cent. solution of bichromate of potassium in water, and a saturated sublimate solution in physiological salt solution. Small thin pieces were excellently fixed in this fluid in 24 hours at the ordinary temperature. Immediately after they were treated with 70—80, 85 and 95° alcohol. The above mixture through the sublimate fixed the nuclei, which action probably takes place owing to the presence of the bichromate

of potassium; whilst the latter salt fixes the hæmoglobin and protoplasmic portion. The tissues are subsequently imbedded in paraffin. Celloidin has not been found useful by most observers.

Staining of sections.—Though we have been acqainted with the spirillum since 1873, it was not till 1879 that it was first successfully demonstrated in sections by Koch ($^{38}_{p.\ 37}$). He succeeded, by means of Vesuvin, in staining the parasite in sections of the brain, lungs, liver, kidneys, spleen, and skin obtained from a monkey which was killed during the attack. A microphotograph of the spirillum in a blood vessel of a liver section made by Koch is given in Pfeiffer's and Franknel's Atlas. Metschnikoff ($^{104}_{p.\ 182}$) used gentian violet for staining sections; Soudakewitch ($^{123}_{p.\ 551}$) used a modification of Kuhne's method as follows: The sections were first stained with boric carmine, after they were placed in Orth's decolourising solution (30 parts water, 70 of alcohol, and 1 part of hydrochloric acid), and subsequently washed with water and left for 12 to 24 hours n a solution of methylene blue. This solution was obtained by adding to a watch glass full of distilled water 3 or 4 drops of a carbolised solution of methylene blue (methylene blue dissolved in 5 per cent. carbolic solution). After removal the sections were plunged for a second into alcohol (95°) which was coloured with methylene blue; next into coloured aniline oil, and subsequently into

uncoloured oil. The sections were finally washed in Cedar oil and mounted in Canada balsam. This method did not produce contrast straining. Soudakewitch did not succeed in staining the spirillum in sections obtained from human organs.

More recently Nikiforoff ($_{\text{p.}213}^{124}$) has not only succeeded in obtaining a contrast stain, but has also successfully stained the parasite in sections of human organs. He succeeded in doing so by the addition of tropeolin or fluorescin to methylene blue solution as follows:—

5 parts of 1 per cent. alcoholic solution of tropeolin.

10 parts of a concentrated watery solution of methylene blue.

10 parts of water.

The mixture is well shaken and for each 25 c.c. 2 to 5 drops of a weak caustic potash solution (1 in 1000) is added. If any sediment forms the solution should be filtered. The sections require to be kept in the solution for some hours (a few hours if the temperature is 36–40C, or 24 hours at the ordinary temperature). After staining, place the sections in water and dip them 2 or 3 times into a solution of equal parts of good absolute alcohol and ether. Transfer after into bergamot oil, and finally into xylol. By this method the nuclei and the spirilla are stained of a pale blue colour, the remaining tissues being of a greenish yellow tint.

Chapter IX.

Pathological changes found in the organs — Abdominal organs.

Spleen.—The changes found in this organ consist of—

(1) a general enlargement;

(2) an accumulation of lymphoid elements in the malpighian bodies;

(3) the presence of hæmorrhagic foci;

The general enlargement is found in almost every case of relapsing fever, the organ even attaining two or three times its normal dimensions. The enlargement commences with the first attack, subsides after crisis, and again increases in size with each subsequent relapse. Carter ($_{p.\,114}^{76}$) says that the spleen enlarged even in the incubation period of an inoculated monkey; and Friedrich ($_{p.\,518}^{55}$) has made a similar observation apparently in man.

The splenic capsule is generally tense, often covered with fibrinous deposit, and occasionally adherent to the diaphragm and other adjacent structures.

On section the spleen is found to be of a brick or dark red colour, fairly firm in texture, and displays a considerable number of whitish or whitish yellow foci produced by the enlarged malpighian bodies. In addition to this, hæmorrhagic infarcts are to be found.

Microscopically, it is found that the general enlargement is produced by an engorgement of the venous sinuses, together with a large increase of the cellular elements of the pulp, the cells as first pointed out by Metschnikoff are often seen in a state of karyokinesis. Nikiforoff gives the following structures as being found in the veins in addition to the ordinary white and red blood cells:—

1. Cells equalling the leucocytes in size with nuclei in which many (six or more) chromatin granules were desintegrated.

2. Large cells larger than the leucocytes with vesicular nuclei and containing one or more red corpuscles.

3. Distinct leucocytes with broken up nuclei and clusters of chromatin granules

The number of polynuclear elements in the veins increase with each attack.

The endothelium of the vessels, especially the veins, is very swollen projecting into the lumen of the vessel, sometimes it is partly, sometimes even completely detached from the vessel wall. The endothelial cells often show signs of degeneration. From the swelling or detachment of the endothelium the lumen of the vessel is considerably diminished in size.

Malpighian corpuscles vary in size from a pin's head to a millet seed, and are surrounded by a

hæmorrhagic ring, or a coagulation zone. The increase in size is due to a proliferation of the lymphoid cells, these are found frequently undergoing indirect division. The degree of cellular aggregations diminishes from the centre to the periphery, the central cells undergo disintegration becoming granular, the nucleus becomes indistinct and will not take nuclear stains, and the cells finally disappear leaving a mass of granules. Surrounding these areas are found often a number of large cells which contain other cells within them, the latter sometimes contain spirilla. Spirilla are frequently found within and between the cells of these lymphatic areas; provided the cellular degeneration has not progressed too far.

Rudnef * called these structures inflammatory lymphomata, Nikiforoff is inclined to think that they are necrotic areas produced by the presence of the spirillum.

Infarcts vary in size from a walnut to a hen's egg, they are generally sharply circumscribed. They appear during each febrile stage undergoing degenerative changes during the apyretic period. Ouskow, Puskhareff and Soudakewitch state that it is possible from the condition of the infarcts to find at what period of the disease the patient has died; for example, a case dying during the first

* Rudnef, Ueber den Typhus, Protocolle des vereins russ aertze 1869-70, p. 216—218.

relapse would have fresh infarcts, with others of a pale colour, showing degenerative changes, which were produced in the first attack.

Whilst writers are agreed as to the presence of these hæmorrhagic foci, there is no unanimity of opinion as to their mode of origin. Some of the older writers attributed them to coagulation of blood in the venous sinuses (Kuttner),* to compression of the blood vessels by the increase of the lymphatic structures, and the confluence of adjacent malpighian corpuscles (Erichsen),† or to their being bloodless areas in the venous sinuses which with their degenerated cellular contents gave the appearance of infarcts (Rudnef). Ponfick, [14] on the other hand, believed them to arise from venous thrombosis, more recently writers have been inclined to believe that there is likely to be more than one mode of origin. Lubimoff [86], for example believes that some are produced by coagulation in the venous sinuses, whilst others are formed by the confluence of adjacent enlarged malpighian bodies. Soudakiwitch [123] believes that they are thrombi produced by the blocking of the small veins with spirilla.

The slowness of the circulation produced by the swollen endothelium of the vessels, especially the

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* Kuttner, Path. Anatomischen Veranderungen in der Febris Recurrens, St Petersburg Med. Zeitschrift, Bd. 8, 1865, p. 113.

† Erichsen, Verhandlungen des Allgemein Vereins, St. Petersburg Aertze Sitzung 16-3-65, St. Petersburg Med. Zeitschrift, Bd. 8, p. 311.

veins, and the uneveness produced by the swollen and sometimes degenerated endothelium offer excellent conditions for the formation of a thrombus. This, as has been stated, was Ponfick's opinion; an opinion which is also shared by Pushkareff and which offers the best explanation of the condition found in the spleen.

The literature of relapsing fever contains numerous cases of rupture of the spleen from the giving way of an infarct situated on the surface of the organ. Cases have been recorded by Greissenger, Kuttner, Zuelzer, Hudson, Pribram and Robitschek, Albrecht, Petersen and Ouskow. Petersen has recorded a case of spontaneous rupture of the spleen with extravasation of blood into the colon.

Abscess of the spleen is occasionally found. It has sometimes been of a pyæmic character and associated with suppuration elsewhere; but there are numerous instances on record where the splenic abscess has been the only seat of suppuration in the body.

The abscess may burst into the peritoneal cavity or may remain confined by adhesions in the neighbourhood of the spleen; occasionally the abscess has burst into one of the neighbouring organs. Greissenger and Lubimoff have described cases in which the abscess opened into the left plural cavity, Kornig and Pushkareff cases opening into the left bronchus, Petrowsky into the left lung, Kuttner

into the colon. Puskhareff has also described a case where the pus was found between the pleura costalis and thoracic wall. Petersen ($_{p.\ 325}^{77}$) mentions that there is a specimen in the St. Petersburg Museum from the epidemic of 1864-1865 labelled "Rupture of a splenic abscess into the fundus of the stomach."

The cause of the formation of abscess in relapsing fever has not yet been satisfactorily explained nor has any bacteriological examination of the pus been hitherto published. The spirillum is not a pyogenic organism, we must therefore consider that suppuration is produced by the entrance of one of the pus forming organisms into one of the splenic infarcts.

Liver.—This organ is generally enlarged, according to Carter in as many as 33 per cent. of all surviving cases. The enlargement commences in the febrile period, diminishing during the apyrexia. The capsule is distended and sometimes covered with lymph.

On section it may appear either congested, or pale and yellowish in colour. The lobular limits are sometimes obscured. The inter-lobular connective tissue is often infiltrated with small cells which often extend along the blood vessels. The intra-lobular capillaries are greatly distended, their endothelium being swollen, cloudy, and granular, by the distension of the vessels, the surrounding liver cells

are compressed. The liver cells are swollen, cloudy and granular, the nucleus being obscured, the outlines of the cells are often indistinct, the cells appearing to merge into one another. The larger arteries and veins possess the swollen granular and partly detached endothelium which is so constantly found in this disease.

Infarcts are occasionally found in the liver, and some authors have described small collections of lymphoid elements.

In cases where jaundice is a prominent symptom, the liver cells are found to contain pigment, and the endothelium of the bile ducts is altered. Kuttner and Erichsen have described evidences of acute liver atrophy in cases accompanied by jaundice in the St. Petersburg Epidemic of 1864-65. The prevalence of jaundice appears to vary in different epidemics. In the Khojak outbreak it was only present in 9·9 per cent. of the cases, and except in one case it was of a very slight character. When jaundice has been very prevalent some writers have described the disease as bilious relapsing fever.

The jaundice has been attributed to catarrhal inflammation of the duodenum (Ponfick) ; to catarrhal inflammation of the biliary ducts (Moczutkowsky) ; to a peri-angiocholitis and foci of coagulation necrosis (Lubimoff).

In rare instances small abscesses have been found in the liver.

Kidneys.—These organs are enlarged, distended with blood, the cortex is pale and often increased in extent, the pyramidal portion is full of blood.

According to Puskhareff there are evidences of an acute glomerulo-nephritis of slight extent. The epithelium of the urinary tubules is swollen and granular with obscured or invisible nucleus. The convoluted tubules may be only affected; and in cases in which the affection extends to the straight tubes or Henle's loops, the most intense changes are to be found in the convoluted tubes. Hyaline casts have been described by Kuttner, and blood casts by Ponfick. The glomerulus as a rule fills up its capsule, the capillaries being distended, and their endothelium swollen and faintly granular. The endothelium of Bowman's capsule is swollen; Ponfick and Lubimoff have described extravasation of blood within the capsule.

The blood vessels show the characteristic changes found elsewhere, namely, swollen granular endothelium projecting into the lumen of the vessel, this is sometimes partly or even completely detached.

Infarcts have been described by Erichsen, and abscess in the cortical portion has been recorded by Kuttner, Erichsen and Lubimoff.

Stomach and Intestines. — Punctiform hæmorrhages and swelling of the follicular structures of the intestines are not uncommon. Carter ($_{p.\,213}^{76}$)

has recorded a fatal case of gastric hæmorrhage. I found melæna in about 6 per cent. of my cases. There is no record of microscopical examination of the digestive tract, but the vascular changes are probably of the same nature as already described.

According to Ouskow there is an enlargement of the retro-peritoneal glands.

Thoracic organs: Heart.—The heart muscle is pale and soft, the muscular fibres are swollen, cloudy and show evidences of granular and fatty degeneration. The capsule of the heart ganglia is thickened, its endothelium swollen, the nerve cells show evidences of albuminous swelling (Puskhareff).

Respiratory tract.—Laryngitis is present in about 5 per cent. of cases. Symptoms of bronchial catarrh I found in no less than 75-8 of my cases. Both croupous and catarrhal pneumonia are not unfrequent. Gangrene of the lung has been known to occur. Little is known of the exact pathological changes found in the lung, but they are probably of the nature of a parenchymatous inflammation. Soudakewitch ($^{123}_{p.\,599}$) saw infarcts in the lung of monkeys, these varied from a pin's head to a cherry stone in size. The presence of vascular changes in the pulmonary vessels would account for the frequency of blood-tinged expectoration which is so commonly met with in relapsing fever cases.

In one of the fatal cases I saw in the Khojak, there was extending from the left epiglottic base to the lower part of the thyroid a large necrotic area, in the centre of which there was an abscess cavity, there was no sign of tubercular or other disease, the right side of the larynx was only slightly œdematous. There were some small pyæmic abscesses in the lungs, and an abscess evidently arising in the cancellous bone of the sternum.

Brain and its membranes.—The dura mater often displays punctiform hæmorrhages on its inner surface, and is occasionally covered with fibrinous deposits. The pia is more or less cloudy and œdematous. Puskhareff says that in about 29·7 per cent. of the cases there is pachymeningitis interna. Hæmorrhages are not uncommonly found on the surface of the brain chiefly at the vertex, Carter found this present in 8 out of 54 cases; the amount varying from 2 to 8 ounces. Puskhareff has recorded a case of hæmorrhage into the frontal convolution, and Carter has also recorded a case of hæmorrhage into the brain followed by inflammatory softening. There are no pathological changes in the nervous matter.

Muscular and osseous structures.—The muscular pains Klebs has suggested are produced probably by the pressure of blocked vessels on the nerves. There is generally a certain amount of granular and fatty degeneration of the muscular fibres.

The changes found in the bone marrow were first carefully investigated by Ponfick [14], who described two forms, namely, a diffuse, and a circumscribed, form; the former consisted of an infiltration of granular cells and fatty granules investing the vessels in such a way as to resemble as if they were surrounded by an opaque membrane, the surrounding medullary tissue being likewise infiltrated with fine fatty granules. The circumscribed form consisted of necrotic foci of desintegration of the medulla. The focal changes are found generally in the epiphysis.

Lubimoff describes the changes in the medulla as consisting of a crowding against each other of the fat cells, the intervening spaces being filled up by distended blood vessels irregularly arranged with lymphoid elements, free red cells, and multinuclear elements.

Inflammation of the parotid, submaxillary, and inguinal glands were very frequently found in the St. Petersburg Epidemic, 1864-65. Murchison saw only one case of parotitis in 600 cases. Carter says that parotitis is found in 2 to 3 per cent. of cases. In the Khojak outbreak I observed 2 cases, one of which suppurated on both sides, in the other case the inflammation subsided without suppuration.

Uterus and fœtus.—Hæmorrhage from the uterus is not unfrequent. According to Murchison and most observers pregnant women almost invariably

abort. This accident is probably the result of hæmorrhage from the maternal vessels.

Spitz ($_{p.\,167}^{49}$) first made the interesting observation that infection could pass to a fœtus in utero. He detected the spirillum in a blood clot found within the cranium of a five months' fœtus, the mother having aborted during the attack. Albrecht ($_{p.\,141}^{45}$) also found living spirilla 38 hours after death in the blood contained in the heart of a seven months' fœtus which had lived for 8 hours. Mamarowski [135] saw spirilla in the blood of the vena cava and in the right auricle of a four month fœtus.

These cases are undoubtedly instances of intra-uterine infection. It has been supposed that the infection has been produced by the spirillum boring its way into the fœtal blood current. The same kind of intra-uterine infection is known to occur in cases of anthrax, and other parasitic diseases, and as this supposed penetration is not then likely, we must look to other possible modes of infection. Small hæmorrhages from the maternal vessels would suffice to produce a communication between the maternal and fœtal vessels.

Organs of sense.—Catarrhal or even suppurative inflammation of the middle ear leading to deafness is found in from 3 to 7 per cent. of cases.

The eye complications are of considerable importance. Before the ophthalmoscope came into

use writers described these to be of two kinds, namely, amaurotic and inflammatory. Among the former were included all conditions accompanied by loss of vision without any objective changes except perhaps dilatation of the pupil, in the latter were included all visible inflammatory conditions. Eye complications are found in from 3 to 11 per cent. of cases.

Conjunctivitis is occasionally found. Blessig in 1867, and Estlander in 1869, called attention to the importance of inflammatory conditions of the uveal tract, and since that time numerous cases have been published by Logetschnikow*, Peltzer†, Hænich, [17] Trompeter, [60] Kramsztyk, [79] and others. Blessig‡ found 4 cases in 127. Luchau ($_{p.\ 24}^{61}$) 4 in 180. Lachmann ($_{p.\ 551}^{48}$) gives 8 cases of irido-choroiditis and 3 of iritis in 186 cases. At present observers are not agreed as to the seat of commencement of the inflammation, some believing that it invariably arises in the ciliary body and thence extends, whilst others believe that it may arise independently in the iris or choroid. From the published cases it appears that the inflammation is of a plastic kind when affecting the iris and ciliary body. Estlander has recorded a severe case in which a mass of lymph filled up the irido-corneal angle, such cases are likely to be

* Logetschnikow, Arch. f. Opth. XXVI, p. 353.

† Peltzer. Berlin Klin Woch, 1872, p. 144.

‡ Blessig, Compte rendu du congress intern d'opth., Paris, 1867.

followed by glaucoma. When the chief seat of inflammation is in the choroid the usual ophthalmoscopic changes of choroiditis are found, the choroiditis generally ends in resolution, but occasionally atrophic patches result.

The cause of this inflammation is not at present known. Blessig believed that it was possibly the result of choroidal thrombosis or embolism ; some have believed it to be produced by the direct action of the spirillum or by toxins developed by it.

A point of considerable importance is the period when this uveal inflammation arises ; in the majority of cases it appears between 2 and 12 weeks after the commencement of the disease, mostly about 4 weeks (Kramsztyk). This alone disposes of the possibility of the *direct* action of the spirillum being the cause of the inflammation, though the changes produced by it in the vascular endothelium may indirectly influence it.

Retinal hæmorrhages are occasionally found. Lachmann has described vitreous opacities found in two cases without inflammatory reaction,—these were probably the result of previous inflammation of the uvea or retina or of hæmorrhage from those membranes.

Optic neuritis has been mentioned by some authors as having occurred during relapsing fever.

BIBLIOGRAPHY.

1873.

1. *C. Obermeier.* Vorkommen feinster, Eine Eigenbewegung Zeigender Faden in Blute von Recurrens kranken. Centralb. f. d. Med. Wissench, No. 10 of 1873, p. 145.
2. *C. Obermeier.* Berlin Klin, Woch, No. 33 of 1873, p. 391. Discussion in the Berlin Medical Society.
3. *F. Engel.* Ueber die Obermeyers'chen Recurrens Spirillen. Berlin Klin. Woch., No 35 of 1873.
4. *C. Obermeier.* Weitere Mittheilungen uber Febris Recurrens, Berlin Klin Woch, No. 38 of 1873, p. 455.
5. *C. Weigert.* Berlin Klin Woch., No. 49 of 1873, p. 589.
6. *Bliesener.* Ueber Febris Recurrens. Dissertat, Berlin, 1873.
7. *Weissenberg.* Die Febris Recurrens bei Kindern. Jahresbr f. Kinderheilkunde VII, Hft. 1, 15th December.
8. *Stephanowitch.* Beitrage zur Febris Recurrens. Military Medical Journal 118 (Rus.)
9. *Nedsvetzki.* Centralb. f. d. Med. Wissensch, 1873, p. 147.

1874.

10. *Litten.* Recurrens Epidemie in Breslau, in Jahre 1872-73. Deut. Archiv. f. Klin Med., Bd. XIII, Hft. 1, 2, 3 of 1874.
11. *Münch.* Moscow Med. Zeitschr, No. 1 of 1874 (Rus.)
12. *Birch Hirschfeld.* Archiv. f. Klin. Med., Bd. XIII, Hft. 3.
13. *Ponfick.* Ueber das Vorkommen abnormer zellen in Blute von Recurrens Kranken. Centralb. f. d. Med. Wissensch, No. 25, p. 385.
14. *Ponfick.* Anatomische Studien uber den Typhosis Recurrens, Virchow's Archiv, Bd. 60.
15. *Weigert.* Berlin Klin Woch, No. 5, p. 57.
16. *Naunym.* Berlin Klin Woch, No. 7 of 1874.
17. *Hœnich.* Die complicationen und Nachkrankheiten der in der Greifswalder med. Klin des Profr. des Mossler behandelten Falle von Typhus Recurrens. Deut. Arch, Klin Med. 1874-75.

18. *Petuchoff.* Notiz uber die Epidemie der Recurrens und des Typhus biliosus in Jakutsk in dem Jahre. Med. Bote No. 37 u 48, 1874 (Rus.)
19. *Reutlinger.* Untersuchungen uber Geschichte, Geographie, und Statistik des Recurrens in Rusland bis zum Jahre 1874. St. Petersburg, 1874 (Rus.)

1875.

20. *Laptschinsky.* Blutkorperchen Zahlungen bei einen Recurrens Kranken. Centralb. f. d. Med. Wissensch, Bd. 13, p. 36.
21. *Erichsen.* St. Petersburg Med. Zeitschrift, p 161.
22. *Djätschensko.* Die Febris Recurrens. Medic Bote Nos. 40, 41, 43, 45—52 (Rus.)
23. *Giergensohn.* Die Recurrens Epidemie in Riga in den Jahren 1865—1875. Archiv. f. Klin Med., Bd. 19.

1876.

24. *J. Moczutkowsky.* Centralb. f. d. Med. Wissensch No. 11, p. 193.
25. *Unterberger.* Febris Recurrens in Kindesalter. Jahresb f. Kinderheilkunde, Bd. X, Hft. 1 and 2.
26. *L. Heydenreich.* Ueber den Schrauben bacterie des Ruckfallstyphus, St. Petersburg Med. Woch., p. 3.
27. *L. Heydenreich.* Ueber den Parasiten in Recurrent Typhus. Inaugural Dissertat, St. Petersburg 1876 (Rus.).
28. *Mannaseim.* St. Petersburg Med. Woch, 1888, p. 81.
29. *C. Weigert.* Bemurkungen uber die Obemeyers'chen Recurrens faden. Deut. Med. Woch, p. 471.
30. *Laskowsky.* Medizinsky Westnik.

1877.

31. *L. Heydenreich.* Klinische und Mikroskopic untersuchungen uber der Parasiten des Ruckfallstyphus. St Petersburg, 1877.

1878.

32. *Albrecht.* St. Petersburg Med. Woch., No. 20 of 1878.
33. *V. Carter.* Lancet, 8th June.

34. *Warschauer.* Febris Recurrens bei Erwachsenen. Allgem Wien, Med. Zeitung Nos. 44—46.

35. *Kannenberg.* Epidemie in the Charité, Berlin. Charité Annalen, 1878.

1879.

36. *L. Reiss.* Deut. Med. Woch, Nos. 8, 51 and 52.

37. *Cohn.* Deut. Med. Woch, No. 16, p. 189.

38. *Koch.* Deut. Med. Woch, No. 25, p. 327.

39. *Muellendorff.* Ueber Ruckfallstyphus nach Beobachtungen in Stadtischen Krankenhaus zu Dresden 1879. Deut. Med. Woch, p. 631.

40. *J. Moczutkowsky.* Deut. Archiv. f. Klin Med., Bd. 24, p. 80.

41. *Albrecht.* St. Petersburg Med. Woch, No. 25.

42. *V. Carter.* Lancet, 7th June and 9th August.

43. *Holsti.* Epidemie in Helsinfors. Nordiskt Med. Archiv, Bd. XI 1, Nos. 13 and 27.

44. *Spitz.* Die Recurrens Epidemie in Breslau in Jahre 1879. Inaugural Dissertat, Breslau, 1879.

1880.

45. *Albrecht.* St. Petersburg Med. Woch No. 1.

46. *Laptschinsky.* Zur Kentniss der Spirochaten. Centralb. f. d. Med Wissensch, Bd. 18, p. 341.

47. *P. Guttmann.* Zur Histologie des Blutes bei Febris Recurrens. Virchow's Archiv., Bd. 80, p. 1.

48. *B. Lachmann.* Klinische and Experimentalle Beobachtungen aus der Recurrens Epidemie in Giessen in 1879-80. Deut. Arch. f. Klin Med., Bd. 27.

49. *Spitz.* Recurrens Epidemie in Breslau. Deut. Arch. f. Klin Med., Bd. 26, p. 139.

50. *Becker.* Berlin Klin Woch, No. 23, p. 328.

50*a*. *Carter.* Transactions of the Royal Medico-Chirurgical Society, vol. lxiii, p. 82.

50*b*. *Lubimoff.* Uber das Biliose Typhoid. Tagesberichte d'arztl ver du Kassan No. 24.

51. *Caspar.* Berlin Klin Woch, No. 23.

52. *Leo.* Berlin Klin Woch., No. 23, p. 334.

53. *Bjednjakowa and Rypdowsky.* St. Petersburg Wratch No. 36 and Corresp. Blatz. f. Schweizer Aerzte No. 24, p. 799.
54. *Knipping.* Beitrage zur Kentniss der Ruckfallstyphus. Deut Archiv. f. Klin Med., Bd. 26, Hft. 1, p. 10.
55. *Friedrich.* Das auftreten der Febris Recurrens in Sud Deutschland. Deut. Archiv. f. Klin Med., Bd. 25, p. 518.
56. *Hermann Schmidt.* Statistiche Mittheilungen ueber Febris Recurrens aus Stadtischen Barackenlazareth. Berlin Klin Woch, p. 728.
57. *Karsten.* Ueber Febris Recurrens nach beobachtungen auf dem Kriegschantplatze in Bulgaria in dem Jahre 1878-79. Inaugural Dissertat. Dorpat, 1880.
58. *Gadnew.* Ueber das biliose typhoid. Medic Bote No. 43 (Rus.).
59. *Kannenberg.* Epidemie in Charité, Berlin, in 1879. Charité Annalen, 1880, p. 232.
60. *J. Trompeter.* Ueber choroiditis nach Febris Recurrens. Klin Monatsb f. Augenheilkunde XVIII, p. 121.
61. *Luchau.* Ueber ohren und Augenerkrankungen bei Febris Recurrens. Virchow's Archiv. Bd. 82, p. 18.

1881.

62. *Koch.* Mittheilung aus d. Kaiserlichen Gesandh. Bd. 1, p. 167.
63. *A. Bockmann.* Ueber die quantitatem Veranderungen der Blutkorperchen in Fieber. Deut. Archiv. f. Klin Med., Bd. 29, p. 503.
64. *R. Albrecht.* Kentniss und Entwicklung der spirochæte Obermeier. Deut. Archiv. f. Klin Med., Bd. 29.
65. *N. Lubimoff.* Zur Pathologischen anatomie des typhus Biliosus. Centralb. f. d. Med. Wissensch, No. 46.
66. *Cohn.* Beitrage z Physiologie der Pflanzen, Hft. 3, p. 128.
67. *C. Weigert.* Zur tecknik der Mikroskopischen Bacterien Untersuchungen, Virchow's Archiv. Bd. 84, p. 292.
68. *Carter.* Transactions of the International Medical Congress in London. Vol. 1.

69. *Ignatowsky.* Zur lehre von den Mikro-organismen des Blutes und Schweisses bei Ruckfallstyphus. Arbeiten der Aertze des Odessaer Stadtkrankenhauses, Lief IV (Rus.).

70. *Wagner.* Ueber Febris Recurrens. Berlin Klin Woch, No. 1, 12th January.

71. *Petrowsky.* Milz abscesse nach Febris Recurrens. Deut. Archiv. f. Klin. Med., Bd. 28, Hft. 4 and 5, p. 391.

72. *Putschin.* Ueber die nieren affection bei Febris Recurrens, Protocolle der Moskauer, Med. Gesselschaft No. 3.

1882.

73. *O. Motschutkowsky.* Uber den Ruckfallstyphus. Deut. Archiv. f. Klin Med., Bd. 30, p. 165.

74. *Sarnow.* Der Ruckfallstyphus in Halle s in Jahre, 1879—81. Inaugural Dissertat. Leipzig 1882.

75. *Meschede.* Recurrens Epidemie 1879-80 nach beobachtungen in der Stadtkrankenstatt zu Koningsberg. Virchow's Archiv., Bd. 87, p. 393.

76. *V. Carter.* Spirillum Fever. London, 1882.

77. *Petersen.* Ueber Milzruptur bei Febris Recurrens. St. Petersburg Med. Woch, Nos. 37 and 38, pp. 317 and 325.

78. *Rybalkin.* Beobachtungen Über Febris Recurrens, Über die Veranderungen der Hautsensibilitat Wahrend des Fieberstadium Dissertat. St. Petersburg, 1882 (Rus.).

79. *Kramstyk.* Affections de l' œil dans la fieve recurrente Gaz lek Warsawa 2, s. 11, pp. 85, 111, 134.

1883.

80. *Kriwoschein.* Ueber die Veranderungen der Leber und milz, bei typhus recurrens. Dissertat St. Petersburg, 1883 (Rus.).

81. *Gandelin.* Ueber der Ruckfallstyphus. Kankasichen medic. Gesselsch No. 36.

82. *Pastor.* Jegened Klin Gazeta No. 22.

1884.

83. *Engel.* Spirochacte Obermeiri Constatirt in Egypt. Berlin Klin Woch, 1884, XXI, p. 749.

84. *Mashkowski* Clinical Notes on Relapsing Typhus Jegened Klin Gaz. St. Petersb. No. IV, pp. 546, 561.
85. *Rona.* Ueber die Veranderung der Hautdecke bei febris Reeurrens. Pest Med. Chir. Presse, XX, p. 1068.
86. *Lubimoff.* Ueber die Path—anatomiseh Veranderungen bei typhus biliosus. Virchow's Arehiv., Bd. 98, and Vratch No. 15.
87. *Mulhausser.* Ueber Spirillen. Virchow's Archiv., Bd. 97, p. 84.
88. *Jaksch.* Wiener Med. Woch, No. 7, p. 186.
89. *Murchison.* Continued Fevers, London.

1885.

90. *Günther.* Ueber die Farbung der Reeurrens Spirillen in Blutpraparaten Fortschr. d. Med. No. 23, p. 755.
91. *Dippe.* Typhus Reeurrens. Deut. Med. Ztg. 1, p. 121.
92. *Halla.* Febris reeurrens. Med. Chir. Centralb. Wien XX, p. 76.
93. *Carter.* Reeent cases of Spirillum Fever. Trans. Med. and Phys. Soeiety, Bombay n s, VI, p. 31.
94. *Jakowski.* Spiroehety Geraezki powrotnej. Gaz. lek Warsawa 2 s, p. 801.
95. *Jaksch.* Med. Chir. Centralb. Wien XX, pp. 484, 496.

1886.

96. *Wolberg.* Relapsing Fever in Children. Gaz. lek Warsawa 25, pp. 854, 887, 905 and 924, also Jahresb f. Kinderh, Leipzig XXVI, p. 222.
97. *Korovitski.* Protok obst. Vraeh Volkynskvi Guber Zhitomeer, p. 46—50.
98. *Jogischess.* Statistieal material concerning Relapsing Typhus. St. Petersburgh 8°, p. 71.
99. *Krause.* Uber enige in der Praxis Vergekommene Falle von Febris Recurrens. Inaugural Dissertat, Wurzburg.

1887.

100. *Brandt.* Reeurrent Fever in Cronstadt. Med. pribook k Morsksbornikn. St. Petersburg, p. 123.

101. *Hottendorff.* Cincin Lancet, clinic n s, XVIII, p. 65.
102. *Antonoff.* Antipyrin and Thallin in Recurrent Typhus. Jegened Klin Gaz St. Petersburg VIII, p. 56.
103. *Puskhareff.* Pathology of Recurrent Fever. Jegened Klin Gaz. VII, p. 61, and the same in a Monograph published by Stasoolevítch 8°36, p.
104. *Metschnikoff.* Ueber den Phagocytenkampf beim Ruckfallstyphus Virchow's Archiv, Bd. 109, p 176.
105. *Wolberg.* Recurrens Fieber bei kindern. Jahresb f. Kinderheilkunde No. 2.
106. *Weigert.* Fortschr der medicin, p. 732.
107. *Nikiforoff.* Wratch No. 8, p. 183, zur frage der Farbung der Spirochæten des Ruckfallstyphus.
108. *Nikiforoff.* Die Patholog anatomische Verandcrungen der milz bei recurrens. Inaugural Dissertat (Rus.).

1888.

109. *Puskhareff.* Zur path. anatomie der Febris Recurrens. Virchow's Archiv., Bd. 113, p. 421.
110. *V. Carter.* Some recent cases of Relapsing Fever. Trans. Med and Phys. Society, Bombay n s, No. XI, p. 21.
111. *Sakharoff.* Protok. d. Sitz d. Kankas Med. Ges. Zir Tiflis No. 11.
112. *Naunym.* Mittheilungen a d Med. Klinik, Koningsberg, p. 300, Leipzig.
113. *Metchnikoff.* Fortschr. der Med, p. 81.
113(*a*). *Lewis.* Report of the Sanitary Commissioner with the Government of India.
114. *Peter.* Fievre a rechutes. France Medicale 1, p. 745.
115. *Sakharoff.* Uber die Aenlichkeit der Malaria Parasiten mit denjenigen der Febris Recurrens. Wratch No. 1.

1890.

116. *Soudakewitch.* Recurrent Typhus and Splenic Fever in Monkeys. Vratcht XI, p. 1131.
117. *Neal.* Relapsing Fever; China Med. Mission Journal IV, p. 245.

118. *Karlinski.* Fortschr d. Med. No. 5.
119. *Paternatzki.* Eine neue method der Erhaltung und Kultur der Obermeyers'chen Spirillen in Blutegeln. Wratch, p 297.
120. *Paternatzki.* Zur Frage uber die Zukumpft der Spirillen un Blute der Ruckfallstyphus Erkranken. Wratch Nos. 6 and 8.
121. *Schwalowski.* Typhus Recurens bei Entmilzen appen Wratch No. 50.
122. *Baumgartnen.* Lehrbuch der Pathologischen, Mykologie, Vol. 11, p. 840, contains a good article.

1891.

123. *Soudakewitch.* Recherches sur la fievre recurrente. Ann. de l'ins Pasteur No. 9, p. 545.
123*a*. *Karlinski.* Fortschr der Med. No. 11.

1892.

124. *Nikiforoff.* Zur Patholog: Histologie der milz bei recurrens. Zeiglers Beitrage z pat anat. Jena, Bd. XII, Hft. 1, p. 206, and Medec Obozrenie Moskau, XXXVII, p. 1145.
125. *Fedoroff.* Path. Anat. der Febris Recurrens Epidemic. St. Petersburg A. Franschel 8°, p. 45.
126. *Baschenow.* Bolitschnoja Gaseta, Botkina No. 41 (Rus.), Extract in Jahresb ueber Path Mikr., p. 365.

1893.

127. *Tictin.* Spleen in Relapsing Fever. Medr. Obozr. Mosk. XL, p. 533.
128. *Mamurowski.* Medr. Oboz. Mosk. XXXVII, p. 935. (Rus.).
129. *Weintal.* Bacteriological Examination of the Blood in Relapsing Fever. Protok Kankazsh Med. Obsh. Tiflis XXIX, p. 169, 186.
130. *Ramanowski.* The Parasite of Relapsing Fever and methods of Staining it. Russk. Med. St. Petersburg XVII, p. 311 (Rus.).
131. *Ouskow.* Archives des Sciences Biologiques, St. Petersburg, p. 81.

1894.

132. *Szwafer.* On Relapsing Fever observed in Warsaw. Medycina, Warszawa, XXII, pp. 49, 65.

133. *Langovoi.* On Typhus Recurrens and its Parasite Med. Oboz. Mosk. XLI, p. 829, and Bolitschnaja Gaseta, Botkina No. 9.

134. *Tictin.* Centralb. f. Bakt. und Parasitenk No. 15, p. 840.

1895.

135. *A. Mamurowski.* Ein fall von intra-uteriner infection mit recurrens. Medic, Obosrenje No. 20.

135*a*. *Lowenthal.* Epidemic in Moskow in 1894. Vratch Zapiski, Moskau II, p. 35, 49.

1896.

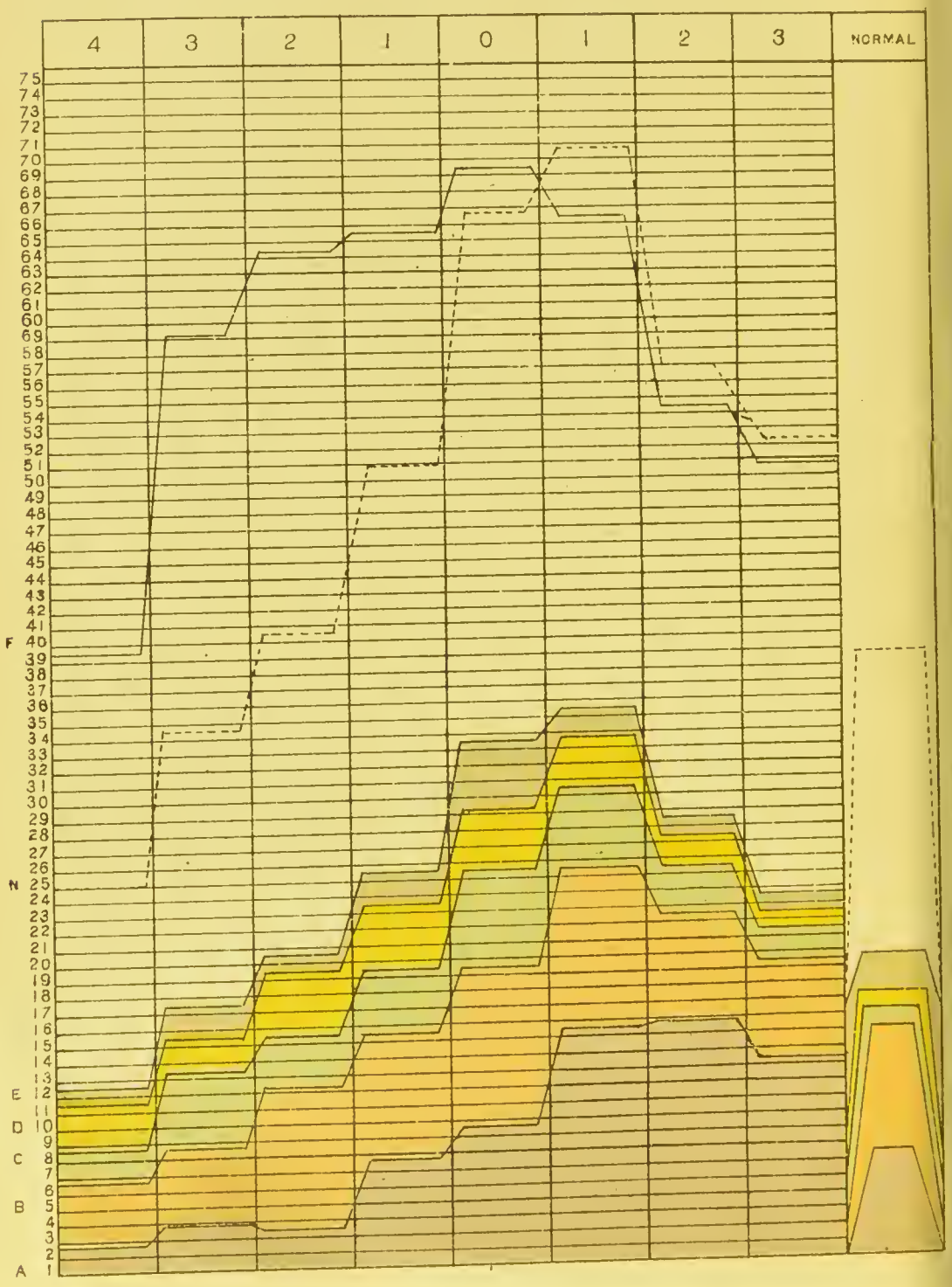
136. *Gorecki.* Etude sur l'irido choroidite de la fievre recurrente. Thèse de Paris No. 260.

137. *Nathauson.* Changes in the Cardiac Ganglia in Relapsing Fever. St. Peterstburgh, Vratch No. 48 of 1896.

PLATE II.

Enumeration of the various forms of leucocytes obtained from observations on 15 patients.

From Ouskow's paper in "Archives des Sciences Biologiques." St. Petersburg, 1893, p. 181.



Explanation of Plate II.

This chart represents the variations of the various cells in relapsing fever, and has been drawn from the average derived from observations on 15 patients. The space O between the vertical lines correspond to the day of crisis, the vertical lines to the left of this indicate the days before crisis, those to the right the days after crisis.

Each coloured column corresponds to a variety of leucocyte ; the height of each indicates the number of cells contained in 1 cubic smillimeter of blood on the different days. The curve *f* corresponds to the number of cells which are most numerous, namely, the polynuclear or old elements (neutrophiles of Ehrlich), it is diminished by half owing to the space which it would otherwise occupy. The distances between the small horizontal lines correspond to 100 cells.

The nomenclature employed is as follows :—

(*a*) small lymphocyte,
(*b*) large lymphocyte,
(*c*) transitional element,
} early forms.

(*d*) mature cells (large mononucleated),
(*e*) lobulated cells
} mature forms.

(*f*) polynuclear elements, old forms (neutrophiles, comprising also the eosinophiles of Ehrlich).

The curve *n* indicates the maximum limit of the imaginary number of the elements as it should be shown daily according to the known quantity of all the other cells. The relation of this curve to the curves *f* gives an exact idea of the increase or decrease per cent. of the old forms at a certain stage of the disease by means of the figure 75 which is their percentage in normal blood.

The vertical space marked "normal" represents the average quantity of each kind of cell in normal individuals, the column of the polynuclear elements being also diminished by half.

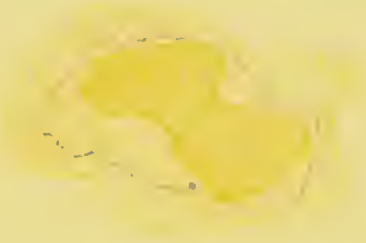
Plate III.

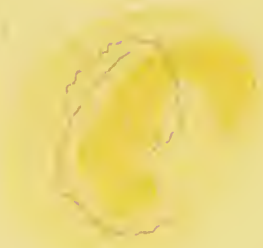
Polynuclear elements of the blood containing spirilla, coloured with gentian violet. Hartnack Apochrom 2·0, Eyepiece IV, from Soudakewitch's paper. (123)

Fig. 1 shows the granulations disseminated in the protoplasm of the leucocyte, and the vacuoles found in the cells.

Fig. 2 shows a straightened out and fragmented spirillum.

Figs. 3 & 4 show the granulations in the course of the spirillum. Fig. 4 shows also a solution of continuity.





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